[^{11}C]Carbon monoxide in the palladium-mediated synthesis of ^{11}C-labelled ketones

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[^{11}C]Carbon monoxide has been used in the palladium-mediated synthesis of [*carbonyl*-^{11}C]ketones. Methyl iodide, vinylic and arylic halides and trifluoromethanesulfonates (triflates) have been coupled with tin reagents with insertion of [^{11}C]carbon monoxide at very low concentrations (10–100 nmol [^{11}C]CO in a total volume of 10 ml). The labelled products are obtained in 36–62% isolated decay-corrected radiochemical yields within 30 min of the end of radionuclide production. In order to use [^{11}C]carbon monoxide efficiently, a gas handling system has been developed which allows the radioactive gas to recirculate through the reaction media. The reactions are performed using a one pot procedure. The best results are achieved with mixed tin reagents containing an unsaturated transferable substituent and $Pd(AsPh_3)_4$. In a typical experiment starting from 25 GBq of [^{11}C]carbon dioxide, 4.2 GBq (47%) of [*carbonyl*-^{11}C]acetophenone 1 is obtained 30 min after the end of radionuclide production. The specific radioactivity of 1 is 91 GBq μmol^{-1}. [*carbonyl*-^{13}C]Benzophenone 6 has been synthesised using the same approach to verify the position of the label.

Introduction

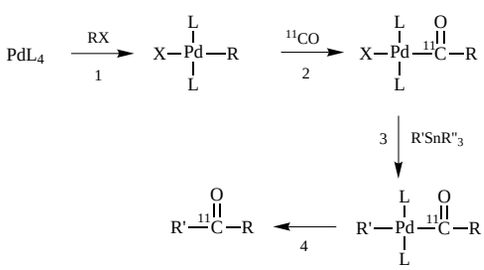
Substances labelled with short-lived positron emitting nuclides can be used with positron emission tomography (PET) and are useful tools in basic and clinical sciences.[1] The radionuclides most frequently used are ^{11}C, ^{15}O and ^{18}F with half-lives of 20.3, 2.07 and 110 min respectively. In order to increase the number of available radiotracers and the possibilities of performing multi-positional labelling, there is a need for new, general labelling methods. Considering the short half-lives of the nuclides used and radiation safety aspects, synthetic radiochemical methods need to be rapid, reliable and suitable for automation.

Although [^{11}C]carbon monoxide was one of the first tracers to be used in human studies,[2] it has been used rarely in labelling reactions and only a few examples are found in the literature.[3] Carbon monoxide usually has a low reactivity in organic synthesis and rather harsh conditions, including high pressures, high temperatures, long reaction times and highly reactive reagents often have to be employed.[4] Thus, [^{11}C]carbon monoxide has not gained much attention as a radioactive precursor for the synthesis of ^{11}C-labelled tracers.

Development of palladium-catalysed carbonylative coupling reactions has provided a mild and efficient tool for the transformation of carbon monoxide into different carbonyl compounds,[5] *e.g.* ketones, aldehydes, esters and amides. These reactions are especially interesting since they can be performed under low carbon monoxide pressure and without the use of polycarbonyl complexes. On account of the low mass involved when high specific radioactivity ^{11}C is used,† a high pressure of [^{11}C]carbon monoxide is difficult to obtain. The use of polycarbonyl complexes in ^{11}C-labelling reactions is unsuitable since it would afford a low yield of labelled product. Furthermore, ^{11}C-polycarbonyl complexes would be difficult to synthesise without isotopic dilution, leading to low specific radioactivities which would be unsuitable for many PET applications.

† Specific radioactivity = radioactivity/mass, typically in the range of 50–500 GBq μmol^{-1}. In a reaction using 1 GBq, the amount of radioactive precursor would be approximately 2–20 nmol.

Recently, a palladium-promoted approach to ^{11}C-labelled ketones was presented where halides were coupled with different tin reagents with the insertion of [^{11}C]carbon monoxide[3d] (Scheme 1). By this method different ketones labelled in the



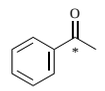
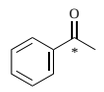
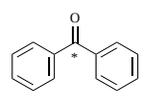
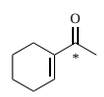
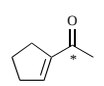
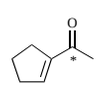
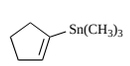
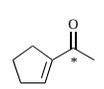
Scheme 1 A mechanistic scheme for the synthesis of [*carbonyl*-^{11}C]ketones from [^{11}C]carbon monoxide,[a] including the four basic steps in the carbonylative cross coupling reaction: 1, oxidative addition; 2, [^{11}C]CO insertion; 3, transmetallation; 4, reductive elimination

carbonyl moiety were synthesised. An interesting application could be the labelling of the 17β-methyl ketone side chain of the D-ring of progestins. [21-^{11}C]Progesterone has earlier been synthesised using [^{11}C]methyl iodide in a carbon alkylation reaction and recently from the 17-acid chloride using a [^{11}C]methyl cuprate.[6] The synthesis of the 17β-methyl ketone side chain of progestins *via* the palladium-catalysed carbonylation reaction has been conducted on the macroscopic scale using halides as substrates.[7] Carbonylation with [^{11}C]carbon monoxide would provide a route to carbonyl labelled compounds and may be advantageous in the ^{11}C-labelling of more sensitive substrates.

Results and discussion

As model compounds, [*carbonyl*-^{11}C]acetophenone **1**, [*carbonyl*-^{11}C]benzophenone **2,** [*carbonyl*-^{11}C]acetone **3**, [*carbonyl*-^{11}C]cyclohexenyl methyl ketone **4** and [*carbonyl*-^{11}C]cyclopentenyl methyl ketone **5** were synthesised *via* a palladium-promoted coupling of a halide or trifluoromethanesulfonate

Table 1 Palladium-mediated synthesis of some [*carbonyl*-^{11}C]ketones from [^{11}C]carbon monoxide[a]

Entry	Substrate	Tin reagent	Palladium complex	*T*/ °C	Product	RY (%)[b]	Isolated RY (%)[c]
1		$Sn(CH_3)_4$	$Pd(PPh_3)_4$	130	 **1**	45–46 (2)	36–37 (2)
2	CH_3I	$SnPhBu_3$	$Pd(AsPh_3)_4$	80	 **1**	53–71 (6)	38–61 (3)
3		$SnPh(CH_3)_3$	$Pd(dppf)_2$	130	 **2**	60–69 (2)	52–58 (2)
4	CH_3I	$Sn(CH_3)_4$	$Pd(PPh_3)_4$	130	 **3**	62–70 (3)	52–62 (3)
5		$Sn(CH_3)_4$	$Pd(AsPh_3)_4$	130	 **4**	37–65 (3)	34–42 (3)
6		$Sn(CH_3)_4$	$Pd(dppf)_2$	130	 **5**	9	—
7		$Sn(CH_3)_4$	$Pd(AsPh_3)_4$	130	 **5**	6	—
8	CH_3I		$Pd(AsPh_3)_4$	80	 **5**	69–70 (2)	53–57 (2)

[a] 45–85 μmol substrate, 15–45 μmol tin reagent and 1.4 μmol of the palladium complex in 300 μl NMP was used, the reaction mixture was heated for 5 min. [b] Radiochemical yield (RY) as determined by HPLC from a sample withdrawn from the reaction mixture. The range is based on (*n*) experiments. [c] Decay corrected isolated yield based on the total amount of radioactivity in the recirculating system.

(triflate) with the appropriate tin reagent with insertion of [^{11}C]carbon monoxide (Table 1). [^{11}C]Carbon monoxide was obtained from [^{11}C]carbon dioxide by reduction over a zinc catalyst at 400 °C. This was conducted either using the Scanditronix RNP-17 radionuclide production system or in a newly developed gas handling system. Nitrogen was used as carrier gas to the gas handling system where it was replaced by helium. The reactions were performed in one pot procedures and analyses were performed by analytical radio-LC and radio-GC.

The gas handling system

A major problem in the previously published investigation was the low trapping efficiency‡ (~10%) of [^{11}C]carbon monoxide in the reaction media.[3d] Carbon monoxide has a low solubility in most organic solvents.[4] Furthermore, when the [^{11}C]carbon monoxide was produced in the Scanditronix system it had to be delivered from the cyclotron vault to the chemistry laboratory in a stream of nitrogen at high flow rates (100–200 ml min^{-1}), which caused the radioactive gas to pass through the reaction media under conditions of low trapping efficiency. To increase the trapping efficiency a gas handling system was developed where [^{11}C]carbon dioxide was locally converted to [^{11}C]carbon monoxide which was delivered at lower flow rates and recirculated through the reaction media (Fig. 1).

In this system [^{11}C]carbon dioxide was trapped and concentrated on a column (Porapak Q, 50/80 mesh, 25 × 2 mm) at −196 °C. Upon heating, the radioactive gas was released in a stream of helium (4–6 ml min^{-1}). Attempts to use a small piece of steel tubing for the trapping of [^{11}C]carbon dioxide resulted in an uncontrolled release of the radioactive gas due to the evaporation of condensed nitrogen. [^{11}C]Carbon dioxide was reduced to [^{11}C]carbon monoxide in a small zinc filled tube (85 × 2 mm, 0.65 g Zn) at 400 °C. The [^{11}C]carbon monoxide was transferred to the recirculation unit *via* ascarite (to trap unconverted [^{11}C]carbon dioxide, usually less than 5%), valve 3 was switched and the pump turned on. The gas was recirculated at 25–30 ml min^{-1} and the total volume of the recirculation unit was 10 ml. After several minutes of recirculation the remaining gaseous radioactivity was transferred to a balloon and the radioactivity of the reaction vial, the silica solid-phase extraction cartridge (SPE) and the balloon was measured. The silica SPE was used to catch volatile products and to protect the pump from solvents.

To evaluate the benefit of the recirculation unit, the synthesis of **1** from [^{11}C]carbon monoxide, phenyl iodide and tetramethyltin was investigated. In these experiments, [^{11}C]carbon monoxide was produced using the Scanditronix system, trapped on a short plug of silica at −196 °C and released in a slow stream of helium upon heating. The drawback with this approach (compared to the local conversion of [^{11}C]carbon dioxide to [^{11}C]carbon monoxide) was that large amounts of the [^{11}C]carbon monoxide (~20–60%) were reoxidised to [^{11}C]carbon dioxide when heated on the silica surface. This prompted the development of the local, small zinc oven.

The recirculation unit increased the trapping efficiency as well as the radiochemical yield as determined by analytical LC from a sample withdrawn from the reaction mixture. This led to an improved radiochemical yield calculated from the total amount of [^{11}C]carbon monoxide (Fig. 2). The results demonstrated that with the recirculation unit, [^{11}C]carbon monoxide could be efficiently used as a radioactive precursor in the synthesis of ^{11}C-labelled radiotracers.

Reaction conditions

The encouraging results on the recirculation unit prompted a

‡ Trapping efficiency, *i.e.* the fraction of radioactivity remaining in the reaction media.

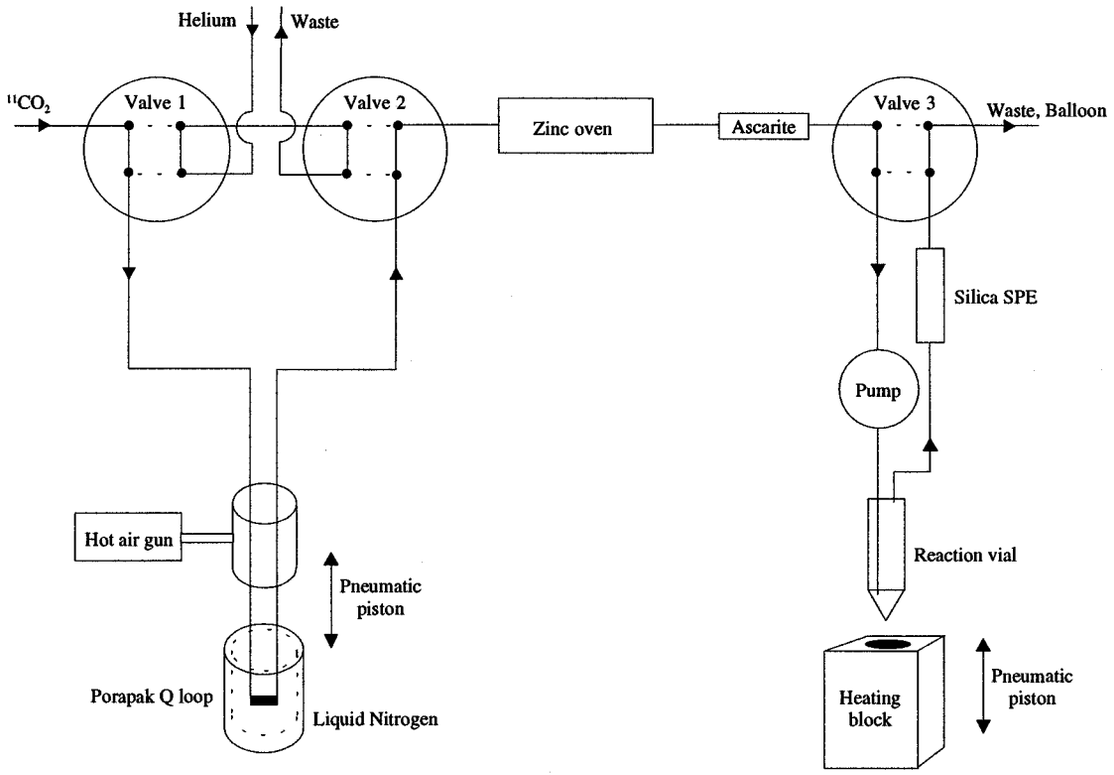


Fig. 1 A gas handling system for the preconcentration of [^{11}C]carbon dioxide followed by conversion to and recirculation of [^{11}C]carbon monoxide

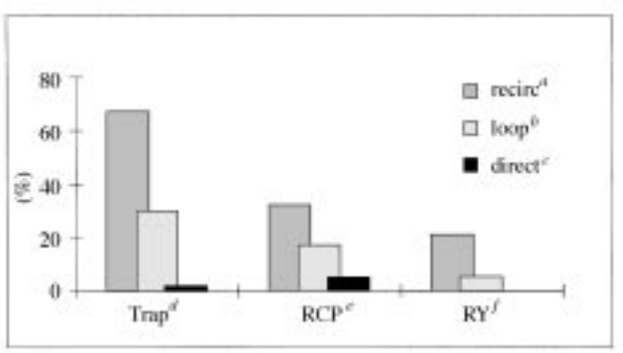


Fig. 2 Effect of the use of a recirculating gas system on the radiochemical yield of [*carbonyl*-^{11}C]acetophenone **1**. The reactions were performed with $Pd(PPh_3)_4$ (1.4 μmol), phenyl iodide (45 μmol) and tetramethyltin (45 μmol) in 300 μl DMSO. The [^{11}C]carbon monoxide was introduced into the reaction mixture at 90 °C and the reaction held at that temperature for 5 min. [a] Performed with the use of the whole recirculating gas system, including both the preconcentration of the [^{11}C]carbon monoxide on the silica loop and the recirculation of the gas phase. [b] Performed only with the preconcentration of the [^{11}C]carbon monoxide on the silica loop and the release with a helium flow of 4 ml min^{-1}. [c] Direct delivery of the [^{11}C]carbon monoxide from the Scanditronix production system. [d] Fraction of the radioactivity trapped in the reaction media. [e] Radiochemical purity of a sample withdrawn from the reaction mixture. [f] Radiochemical yield described as Trap × RCP

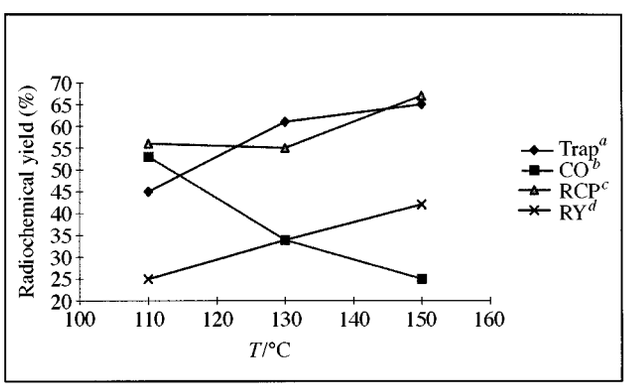


Fig. 3 Temperature dependence of [*carbonyl*-^{11}C]acetophenone **1** radiochemical yield. The reactions were performed with $Pd(PPh_3)_4$ (1.4 μmol), phenyl iodide (45 μmol) and tetramethyltin (45 μmol), in 300 μl NMP. The [^{11}C]carbon monoxide was introduced into the reaction mixture at room temperature and the reactions were heated for 5 min. [a] Fraction of the radioactivity trapped in the reaction media. [b] Residual [^{11}C]carbon monoxide after the reaction. [c] Radiochemical purity of a sample withdrawn from the reaction mixture. [d] Radiochemical yield described as Trap × RCP

re-examination of the factors governing the outcome of the palladium-promoted ^{11}C-carbonylation reaction. As reported,[3d] the use of polar aprotic solvents, *e.g. N*-methylpiperidin-2-one (NMP) and dimethyl sulfoxide (DMSO), gave the best results while the use of ethers, *e.g.* tetrahydrofuran (THF) and 1,4-dioxane, gave lower radiochemical yields. These results concur with those reported by Farina on the Stille coupling.[8] Although the use of DMSO resulted in a higher consumption of [^{11}C]carbon monoxide, it also resulted in more by-products compared to NMP. Furthermore, NMP could be used at higher temperatures and was the solvent selected.

The rate-determining step in palladium-catalysed coupling reactions is usually the transmetallation[8] (Scheme 1, step 3). While CO insertion has been reported to be facile at temperatures as low as −20 °C, the transmetallation step often requires temperatures above 100 °C and long reaction times when unreactive tin reagents, *i.e.* tetraalkyltin reagents, are employed. The temperature dependence of the [*carbonyl*-^{11}C]-acetophenone **1** synthesis from phenyl iodide and tetramethyltin was examined (Fig. 3). The results indicated that temperatures higher than 150 °C might be used when thermally stable substrates and palladium complexes are employed. However, in order to enable evaluation of the effect of changes in parameters other than the temperature on the radiochemical yield, a reaction temperature of 130 °C was selected. The use of reagents that promote a faster transmetallation enabled the use of lower reaction temperatures. Hence, the formation of **1** from methyl iodide and phenyl(tributyl)tin was rapid at 80 °C while

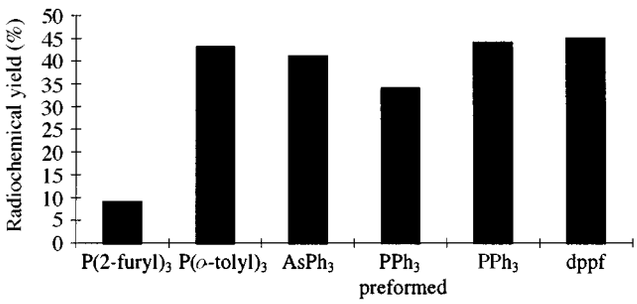


Fig. 4 Radiochemical yields of [*carbonyl*-^{11}C]acetophenone **1** using different ligands. The reactions were performed with *in situ* generation of the palladium complex from $Pd_2dba_3{\cdot}CHCl_3$ (0.7 mg, 0.7 μmol), and ligand (4 equiv., 5.6 μmol) in 300 μl NMP. An exception was the use of commercially available $Pd(PPh_3)_4$ (preformed, 1.4 μmol). Phenyl iodide (45 μmol), tetramethyltin (45 μmol) and [^{11}C]carbon monoxide were introduced into the reaction mixture at room temperature and the reaction mixtures were heated for 5 min at 130 °C. Radiochemical yields are described as trap × radiochemical purity (RCP) of a sample withdrawn from the reaction mixture.

the corresponding transformation from phenyl iodide and tetramethyltin required a longer reaction time and a reaction temperature of 130 °C.

Choice of catalyst

Oxidative addition–transmetallation sequences have previously been reported to be rather tolerant with regard to the choice of catalyst.[9] This was also experienced in ^{11}C carbonylations using tetraalkyltin compounds. In the present investigation the active catalyst was usually generated *in situ* from tris(dibenzylideneacetone)dipalladium chloroform adduct ($Pd_2dba_3{\cdot}CHCl_3$) and four equivalents of ligand. In the synthesis of **1**, five out of six catalysts gave similar results (Fig. 4). The residual amount of unreacted [^{11}C]carbon monoxide varied from 1% [Pd($AsPh_3$)$_4$] to 34% [preformed $Pd(PPh_3)_4$]. In addition to **1**, formation of [*carbonyl*-^{11}C]benzophenone was observed. The additional phenyl group probably originated from the phosphine or arsine used as ligand. This scrambling, which was observed in all experiments, is a phenomenon which was recently reported by Morita *et al.* and Segelstein *et al.*[10] The radiochemical yield of the by-product was typically 10–25%. An increased amount of added catalyst, as well as elevated reaction temperature, was found to increase the relative amount of this by-product.

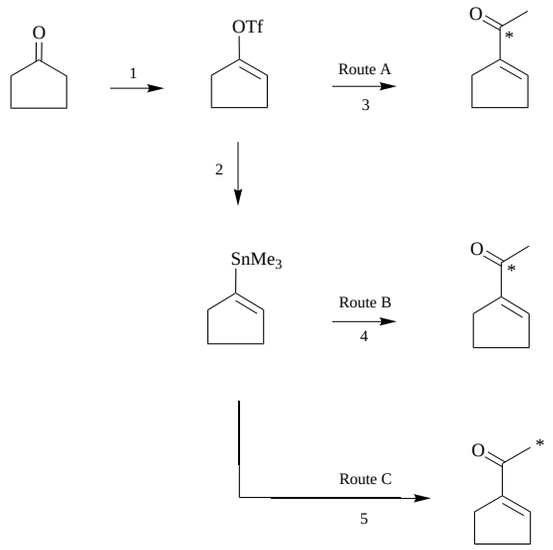
The choice of catalyst was found to be crucial when triflates were used as substrates. The radiochemical yield of **4** was doubled with the use of $AsPh_3$ as the ligand as compared to other ligands. $AsPh_3$ has been used to facilitate the rate-determining transmetallation in the Stille coupling.[8] This ligand enhances the rate of the reaction and simultaneously reduces the free ligand inhibition observed with more electron donating ligands. The increased radiochemical yield probably reflected faster product formation, allowing a higher conversion of cyclohexenyl triflate to **4** before the triflate and/or the catalyst decomposed.

Stoichiometry

On account of the high specific radioactivity, 10–100 nmol of [^{11}C]carbon monoxide in a total volume of the recirculation unit of 10 ml was used in this study. The maximum partial pressure of [^{11}C]carbon monoxide was calculated to be 2.5–25 Pa (2.5×10^{-4} to 2.5×10^{-3} atm). Although many palladium-catalysed carbonylation reactions are performed under atmospheric or elevated pressure of carbon monoxide, synthesis of ^{11}C-labelled ketones could be efficiently conducted using this low pressure of [^{11}C]carbon monoxide. Due to limited availability of precursor and a desire for high specific radioactivity product, small scale synthesis is desirable. When less than 20 μmol (67 mM) phenyl iodide was used, the radiochemical yield of **1** from phenyl iodide and trimethyltin was diminished. The amount of tin reagent added did not seem to have a large impact on the radiochemical yield of **5** from cyclopentenyl(trimethyl)tin and methyl iodide, *e.g.* 15–45 μmol (0.05–0.15 M) cyclopentenyl(trimethyl)tin was used without affecting the radiochemical yield. The amount of catalyst could be varied from 0.5 to 6 μmol (1.7–20 mM) without any effect on the radiochemical yield of **1** from phenyl iodide and tetramethyltin.

Synthetic strategy

In the synthesis of ^{11}C-labelled methyl ketones there are alternative routes available (Scheme 2). Either the methyl group



Scheme 2 Alternative routes for the synthesis of ^{11}C-labelled cyclopentenyl methyl ketone. *Reagents:* 1, Tf_2O, 2,6-dimethylpyridine, CH_2Cl_2; 2, Sn_2Me_6, $Pd(PPh_3)_4$, THF; 3, [^{11}C]CO, $SnMe_4$, $Pd(dppf)_2$, NMP; 4, [^{11}C]CO, CH_3I, $Pd(AsPh_3)_4$, NMP; 5, [^{11}C]CH_3I, CO, $Pd(PPh_3)_4$, 1,4-dioxane.

originates from the tin compound, *i.e.* tetramethyltin (route A); or the methyl group originates from methyl iodide (route B). Since the rate limiting step usually is the transmetallation, any factor that facilitates this step may allow the reaction to be run under milder conditions. In the synthesis of **5** (Table 1, entries 6–8), route A (tetramethyltin and cyclopentenyl triflate) was unable to provide the labelled product in a radiochemical yield exceeding 10%, whereas route B [cyclopentenyl(trimethyl)tin and methyl iodide] resulted in a radiochemical yield of 70% (55% isolated). The transfer of a cyclopentenyl group instead of a methyl group from tin to palladium enhanced the rate of the transmetallation and the reaction could be performed at 80 °C. The transfer rate for different groups from tin to palladium is in the order: alkynyl > alkenyl > aryl > benzyl > alkyl.[9,11] Attempts to facilitate the transmetallation by the use of $Pd(AsPh_3)_4$ failed (entry 7), probably due to thermal instability of the triflate.

Labelling in different positions is a tool to get more detailed information on various physiological processes with PET.[12] The procedure presented here resulted in ^{11}C-carbonyl labelled ketones, whereas the use of [^{11}C]methyl iodide, carbon monoxide and an organotin reagent would produce the [^{11}C]methyl ketone instead[13] (route C, Scheme 2). This approach was studied in a few experiments, yielding 15% of the cyclopentenyl [^{11}C]methyl ketone using preformed $Pd(PPh_3)_4$ in dioxane.§

§ 1.3 mg (1.2 μmol) $Pd(PPh_3)_4$, 300 μl 1,4-dioxane and [^{11}C]CH_3I in 100 μl THF. Sparged with CO for 30 s, 2μl (10 μmol) Sn(cyclopentenyl)$(CH_3)_3$, 120 °C, 8 min. The radiochemical yield is given as the radiochemical purity of a sample withdrawn from the reaction mixture.

All three routes are available from the same starting material. Route B may be the first choice where ^{11}C-carbonylations are concerned. The use of milder reaction conditions and the possibility of using less of the substrate are good arguments for this route. Route A saves one synthetic step in the laboratory and can be considered when robust substrates are employed. Route A and B involve the use of [^{11}C]carbon monoxide which could give a higher specific radioactivity compared to the use of [^{11}C]methyl iodide which is employed in route C.

Characterisation

The identities of ^{11}C-labelled products were assessed with analytical reversed phase LC before and after addition of unlabelled reference material. The radioactivity that remained in the gaseous phase was analysed using Radio-GC with unlabelled reference and found to be unreacted [^{11}C]carbon monoxide. [*carbonyl*-^{11}C]Benzophenone **2** was also characterised by ^{13}C-NMR analysis of [*carbonyl*-^{13}C]benzophenone **6** synthesised by the same method as that used for [*carbonyl*-^{11}C]benzophenone with the simultaneous addition of [^{13}C]carbon monoxide and [^{11}C]carbon monoxide. The ^{13}C NMR signal at 196.7 ppm corresponded to the ^{13}C signal from the carbonyl carbon of authentic benzophenone. The material **6** was further analysed on LC-MS and the molecular mass (*m*/*z* 184, M + 1) was found to be one mass unit over the molecular mass of authentic benzophenone (*m*/*z* 183, M + 1).

Conclusions

[^{11}C]Carbon monoxide at very low concentrations was used in the palladium-promoted carbonylative coupling of organic halides and triflates with organotin compounds. This is a versatile method for the production of ketones ^{11}C-labelled in the carbonyl moiety. Using this approach vinylic or arylic ^{11}C-labelled methyl ketones, *e.g.* [*carbonyl*-^{11}C]acetophenone **1** and [*carbonyl*-^{11}C]cyclopentenyl methyl ketone **5**, as well as ^{11}C-labelled ketones containing two unsaturated groups, *e.g.* [*carbonyl*-^{11}C]benzophenone **2,** can be synthesised in good radiochemical yields. 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-labelled ketones. The use of [^{13}C]carbon monoxide in the same method enables the synthesis of different carbonyl ^{13}C-labelled ketones.

Experimental

General

[^{11}C]Carbon dioxide production was performed using a Scanditronix MC-17 cyclotron by the ^{14}N(p,α)^{11}C nuclear reaction. A nitrogen (AGA Nitrogen 6.0) gas target containing 0.1% oxygen (AGA Oxygen 4.8) was used.

Analytical LC was performed on a Beckman system equipped with a Beckman 126 pump, a Beckman 168 UV detector in series with a β^+-flow detector and a Beckman C-18 ultrasphere ODS column, 5 μm, 250 × 4.6 mm (id). A Gilson 231 was used as autoinjector.

Preparative LC was performed on an identical Beckman system, equipped with a Beckman ultrasphere ODS column, 250 × 10 mm (id). Synthia, a robotic system for production of radiopharmaceuticals,[14] was used for injection and fraction collection. Mobile phases used for analytical and preparative LC were: 0.05 M ammonium formate pH 3.5 (A), 0.01 M potassium dihydrogen phosphate (B) and acetonitrile–water (50 : 7) (C).

Radio-GC was performed on a Shimadzu GC-A14 with TCD detection in series with a β^+-flow detector. An Alltech CTR column was used. Conditions were as follows: column temp. 35 °C, injection temp. 50 °C, TCD temp. 70 °C, TCD current 150 mA, carrier gas He at 60 ml min^{-1}. Data were collected and analysed with Beckman system Gold software. Radioactivity was measured in an ion chamber, Veenstra Instrumenten bv, VDC-202.

Phenyl iodide was distilled and methyl iodide was used as received (Aldrich). Cyclohexenyl and cyclopentenyl triflates were synthesised from the corresponding cycloalkanones according to published procedures.[15] Tetramethyltin and phenyl(tributyl)tin were purchased from Aldrich and used as received. Cyclopentenyl(trimethyl)tin was synthesised from cyclopentenyl triflate as described.[16] The palladium complexes were generated *in situ* from tris(dibenzylideneacetone)-dipalladium chloroform adduct (Aldrich) and the appropriate ligand. Ligands were purchased from Lancaster or Aldrich and used as received. Tetrakis(triphenylphosphine)palladium was purchased from Lancaster.

N-Methylpiperidin-2-one, NMP, was distilled over calcium hydride before use. Anhydrous dimethyl sulfoxide, DMSO, was purchased (Aldrich Sure/Seal) and used as received. Ethereal solvents were freshly distilled before use.

Acetophenone, benzophenone and acetone were purchased, while cyclohexenyl methyl ketone and cyclopentenyl methyl ketone were synthesised *via* Friedel–Crafts acylations on the corresponding cycloalkenes.[17]

Identities of synthesised materials were determined using ^{1}H and ^{13}C NMR spectroscopy and GC–MS. NMR spectra were recorded on a Varian XL 300 (300 MHz) or a Varian Gemini spectrometer (200 MHz). Tetramethylsilane or chloroform[^{2}H] was used as internal standard. GC–MS was performed with GC separations on a Varian 3400 GC. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument with electron impact ionisation at 70 MeV. LC–MS was performed using a Micromass VG Quattro with positive atmospheric pressure chemical ionisation (APcI$^+$). A Beckman 126 pump, a CMA 240 autosampler and a Beckman Ultrasphere ODS C_{18} (5 μm, 250 × 4.6 mm id) column were used. Mobile phase was water–methanol (20 : 80), 1 ml min^{-1}.

The gas handling system was built using Valco AC4W valves, VICI AG, a Leister typ-700 heat gun and a KNF Neuberger NMP 30 KVDC pump. Porapak Q 50/80 was purchased from Supelco and silica gel 100/120 from Alltech.

Methyl [*carbonyl*-^{11}C]ketones from tetramethyltin

Pd_2dba_3·$CHCl_3$ (0.7 mg, 0.7 μmol) and ligand (4 equiv., 5.6 μmol) were dissolved in 300 μl NMP at room temperature. The solution was conditioned by degassing with helium and kept under a helium atmosphere during the entire reaction. The halide or triflate (45–85 μmol) was added and the [^{11}C]carbon monoxide was introduced into the recirculation unit. When the radioactive gas had been trapped, the system was closed and the pump turned on. Tetramethyltin (45 μmol) was added and the reaction mixture was heated for 5 min at 130 °C while recirculating the [^{11}C]carbon monoxide. At the end of recirculation, the heating bath was removed and radioactivity remaining in the gas phase was transferred into a balloon using a stream of helium. The radioactivity in the gaseous phase, the silica guard column and the reaction mixture was measured. The reaction mixture was purified by preparative LC: solvent A–C (50 : 50) isocratic elution 0–5 min, linear gradient to 0 : 100, 5–10 min, flow 5 ml min^{-1}. The identity and radiochemical purity of the collected fractions were assessed by analytical LC: solvent A–C (60 : 40) isocratic elution 0–5 min, linear gradient to 10 : 90, 5–8 min, flow 2 ml min^{-1}, wavelength 254 nm, retention times (t_r) of **1, 4** and **5** were 4.6, 6.7 and 3.9 min respectively.

Methyl [*carbonyl*-^{11}C]ketones from methyl iodide

The syntheses were carried out as described for the synthesis of methyl [*carbonyl*-^{11}C]ketones from tetramethyltin with the following changes: methyl iodide (85 μmol) and tin reagent (15–45 μmol) were used and the reaction mixture was heated at 80 °C.

[*carbonyl*-^{11}C]Benzophenone 2

The synthesis was carried out as described for the synthesis of methyl [*carbonyl*-^{11}C]ketones from tetramethyltin with the following changes: diphenylphosphinoferrocene (dppf) (1.6 mg, 2.8 μmol) was used as ligand. Phenyl iodide (5 μl, 45 μmol) and phenyl(tributyl)tin (8 μl, 45 μmol) were used and the reaction mixture was heated at 80 °C. The reaction mixture was purified by preparative LC: solvent A–C (50:50) isocratic elution 0–5 min, linear gradient to 0:100, 5–10 min, flow 5 ml min^{-1}. The identity and radiochemical purity of the collected fractions were assessed by analytical LC: solvent A–C (60:40) isocratic elution 0–5 min, linear gradient to 10:90, 5–8 min, flow 2 ml min^{-1}, wavelength 254 nm, retention time of **2** was 9.6 min.

[*carbonyl*-^{11}C]Acetone 3

The synthesis was carried out as described for the synthesis of methyl [*carbonyl*-^{11}C]ketones from tetramethyltin with the following changes; PPh_3 (1.5 mg, 5.6 μmol) was used as ligand and methyl iodide (85 μmol) as substrate. Most of the product **3** distilled from the reaction mixture and was caught in the silica guard column, which after the reaction was eluted with 2 ml of LC eluent into the reaction mixture. The resulting solution was purified on preparative LC: Solvent B–C (98:2) isocratic elution 0–5 min, linear gradient to 0:100, 5–10 min, flow 5 ml min^{-1}. The identity and radiochemical purity of the collected fractions were assessed by analytical LC: solvent B–C (95:5) isocratic elution 0–5 min flow 1 ml min^{-1}, linear gradient to 5:95, 5–15 min, flow 2 ml min^{-1}, wavelength 260 nm, retention time of **3** was 4.9 min.

[*carbonyl*-^{13}C]Benzophenone 6

As described for [*carbonyl*-^{11}C]benzophenone **2** with the following changes: $Pd_2dba_3{\cdot}CHCl_3$ (1.4 mg, 1.4 μmol), $AsPh_3$ (3.4 mg, 5.6 μmol), phenyl iodide (20 μl, 180 μmol) and phenyl(tributyl)tin (40 μl, 225 μmol) were used. [^{13}C]Carbon monoxide (5 ml, 225 μmol) was slowly added *via* syringe after the addition of the tin reagent.

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