Synthesis of ^{11}C-Labelled Ketones *via* Carbonylative Coupling Reactions using [^{11}C]Carbon Monoxide

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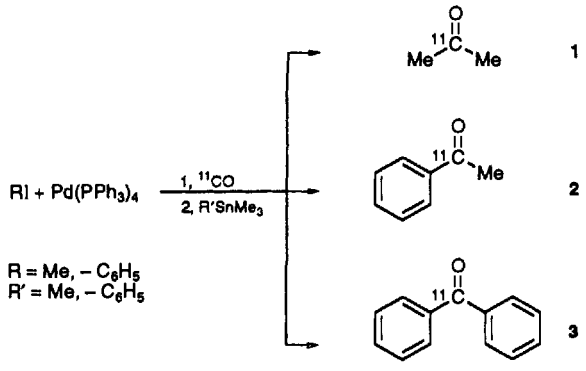
Ketones, labelled with ^{11}C in the carbonyl position, were synthesised by the use of [^{11}C]carbon monoxide in palladium-promoted carbonylative coupling reactions of organic halides with organotin reagents. 100–300 MBq of compounds **1–3** were obtained within 30 min after the end of bombardment, starting from approximately 1000 MBq [^{11}C]carbon monoxide, and the decay-corrected radiochemical yields were in the range 25–50% based on the [^{11}C]carbon monoxide.

The use of compounds labelled with β^+-emitting nuclides such as ^{11}C (half-life of 20.3 min) in positron emission tomography (PET) is a powerful technique for *in vivo* investigations of biologically interesting compounds.[1] The advancement of PET as an important tool in the medical and pharmaceutical sciences has created an increased demand for tracers labelled with short-lived radionuclides, and thus a corresponding need for synthetic methods suitable for the rapid incorporation of such nuclides into various target molecules. Development of new synthetic procedures, compatible with the high specific radioactivity of the ^{11}C-labelled precursors used† and with the limited synthesis time available,[2] is therefore essential. An extended arsenal of methods for ^{11}C synthesis will, in addition, provide further possibilities to label a specific tracer in different positions, thereby enabling more detailed investigations of various physiological processes.[3]

Although [^{11}C]carbon monoxide is a readily available ^{11}C-precursor, only a few examples on the application of [^{11}C]carbon monoxide in labelling synthesis are described in the literature.[4] Many carbonylation reactions require long reaction times and a high pressure of carbon monoxide, and their usefulness in ^{11}C synthesis have therefore been somewhat restricted. During the last decade, however, the use of palladium-catalysed carbonylative coupling reactions of electrophiles with various organometallic reagents, or with other nucleophiles, have proven to be mild and efficient methods for the formation of different carbonyl compounds, *e.g.* ketones, amides and esters.[5] The versatility of palladium-assisted labelling reactions has recently been demonstrated in synthesis of ^{11}C-labelled nitriles[6] and benzamides,[7] employing hydrogen [^{11}C]cyanide as the labelled precursor. In the present paper, the use of [^{11}C]carbon monoxide in palladium(0)-promoted carbonylation reactions is reported.[8] The labelling reaction was investigated utilising the carbonylative coupling of organic halides with organotin compounds[9] in the synthesis of some model ketones (Scheme 1).

The [2-^{11}C]acetone **1**, [*carbonyl*-^{11}C]acetophenone **2** and [*carbonyl*-^{11}C]benzophenone **3** were synthesised using a one-pot procedure, in which cyclotron-produced [^{11}C]carbon dioxide was reduced on-line to [^{11}C]carbon monoxide and transferred directly to the reaction vessel using nitrogen gas as the carrier. The [^{11}C]carbon monoxide was bubbled through a mixture of a halide, tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] and solvent, and after addition of an organotin



Scheme 1

compound the reaction vessel was heated at 90 °C for 4 min. The radiochemical yields of ^{11}C-labelled ketones **1–3** were in the range 62–82% (Table 1), as determined by HPLC analyses of samples withdrawn from the reaction mixture. Although a prolonged reaction time resulted in an increased radiochemical yield in the reaction, the decay of ^{11}C has to be considered, and the final yield of isolated product may therefore not be improved by such measures.[10]

Due to the high specific radioactivity of the ^{11}C precursor, the amount of carbon monoxide used in these reactions was approximately 1–20 nmol. The other reagents were present in large excess, and usually 0.5 μmol of $Pd(PPh_3)_4$ and 15 μmol of the halide and the organostannane were employed. A lower radiochemical yield of compound **2** was obtained when the amount of halide and organostannane was reduced, *e.g.*, a 1 : 1 : 1 molar ratio of $Pd(PPh_3)_4$, halide and organotin reagent (0.5 μmol scale) resulted in a 35% radiochemical yield as compared to 80% using a 1 : 30 : 30 molar ratio. Side-product formation arising from cross-coupling between the halide and the organotin reagent is not a problem in these reactions, provided that the labelled product during the work-up procedure can be efficiently separated from such cross-coupling products by suitable chromatographic techniques.

The choice of solvent in the carbonylative coupling reactions has, in some cases, been reported to be crucial,[11] and in the synthesis of ^{11}C-labelled ketones the solvent had a dramatic influence on the radiochemical yield. Among the solvents investigated, dimethyl sulfoxide (DMSO) was the most favourable and a 60–80% radiochemical yield of compounds **1–3** was obtained. In dimethylformamide (DMF), the radiochemical yield was in the order of 35%, and when tetrahydrofuran (THF) was used as solvent less than 10% yield of

† Typically in the range of 50–500 GBq μmol^{-1} (1.3–13 Ci μmol^{-1}). In a reaction using 1 GBq, the amount of precursor would be approximately 2–20 nmol.

Table 1 [^{11}C]Carbon monoxide in carbonylative coupling of halides with organostannanes.[a]

R-I	R'-SnMe$_3$	Product	Radiochemical yield (%)[b]
Me	Me	[2-^{11}C]acetone **1**	62 ± 7
Me	C_6H_5	[*carbonyl*-^{11}C]acetophenone **2**	72 ± 7
C_6H_5	Me	[*carbonyl*-^{11}C]acetophenone **2**	83 ± 4
C_6H_5	C_6H_5	[*carbonyl*-^{11}C]benzophenone **3**	82 ± 3

[a] Halide (15 μmol), $Pd(PPh_3)_4$ (0.5 μmol) and tin compound (15 μmol) in DMSO (0.3 cm^3). Reaction time 4 min and reaction temperature 90 °C. [b] Mean value ± range for $n = 3$, determined by analytical HPLC as the percentage of the total amount of radioactivity in a sample withdrawn from the reaction mixture.

the labelled products were obtained. An interesting effect was observed when altering the relative ratio of the reagents employed. By carbonylative coupling of [^{11}C]methyl iodide[12] with tetramethyltin or phenyltrimethyltin, using unlabelled carbon monoxide, formation of [α-^{11}C]acetone or [α-^{11}C]-acetophenone was achieved.‡ In these reactions, a reversed solvent dependence was noticed as the couplings performed in THF afforded the ^{11}C-labelled products in 93–95% radiochemical yield, while less than 30% were obtained in the reactions conducted in DMSO. The possibility of using either [^{11}C]carbon monoxide or [^{11}C]methyl iodide in similar carbonylation reactions provides a versatile method for the synthesis of methyl ketones specifically labelled in different positions.[13]

In the reactions with [^{11}C]carbon monoxide, the amount of radioactivity trapped in the reaction vessel was rather low, *i.e.* approximately 10% of the total amount of radioactivity bubbled through the reaction mixture. The use of low temperature techniques for trapping of the labelled gas[14] may, however, be more efficient in the applications discussed herein, and development of improved methods for manipulation of [^{11}C]carbon monoxide is now in progress.

The majority of the reactions described in this work were conducted using small quantities (approximately 200 MBq) of [^{11}C]carbon monoxide. In order to demonstrate the possible application of this method in production of ^{11}C-tracers for PET, a few experiments using larger quantities of labelled precursor were performed. Starting from 1200 MBq of [^{11}C]-carbon monoxide, 250 MBq of isolated product **1** was obtained within 30 min after the end of bombardment. Approximately 100 MBq of product **2** or **3** was obtained with the same synthesis time, starting from 650–900 MBq [^{11}C]carbon monoxide (purification procedures not optimised). The identity of the ^{11}C-labelled products was determined by radio-HPLC analyses before and after addition of authentic reference substances using two different analytical systems. To ensure that all of the radioactive substance injected into the columns was eluted, the radioactivity in the injected volume and in the collected fractions were compared. Further verification of the product identity of compound **3** was obtained by radio–GLC analyses of the isolated product.

The results presented in this communication demonstrate that efficient synthesis of ^{11}C-labelled ketones can be accomplished using [^{11}C]carbon monoxide in carbonylative coupling reactions of halides with organotin compounds. Since the use of organostannanes in such reactions generally is compatible with a wide range of functional groups in either coupling partner,[9b] this new ^{11}C-labelling method may be useful in the production of more complex ^{11}C-tracers. Further investigation on the application of palladium-promoted carbonylation reactions in formation of ^{11}C-labelled ketones, acids, amides and esters is now in progress.

‡ [^{11}C]Methyl iodide (nmol amounts) was trapped in a mixture of $Pd(PPh_3)_4$ (0.6 mg, 0.5 μmol) and solvent (300 mm^3). After trapping, carbon monoxide was bubbled through the mixture for 20 s and then the organotin reagent (15 μmol) was added. The reaction vessel was heated at 90 °C for 4 min.

Experimental

[^{11}C]Carbon dioxide was prepared by the ^{14}N(p,α)^{11}C nuclear reaction using a nitrogen gas target and 17 MeV protons produced by the Scanditronix MC-17 Cyclotron at the Uppsala University PET Centre. The [^{11}C]carbon dioxide was converted into [^{11}C]carbon monoxide over a zinc catalyst at 400 °C,[14] using the Scanditronix RNP-17 radionuclide production system. The radiochemical purity of [^{11}C]carbon monoxide was >99% (radio–GLC analyses). HPLC was performed with a Beckman 126 pump and a Beckman 166 UV detector in series with a β$^+$-flow detector. GLC was conducted using a Shimadzu GC-14 chromatograph connected to a Raytest Raga-93 radiodetector. Phenyltrimethyltin, tetrakis-(triphenylphosphine)palladium and tetramethyltin were purchased from Aldrich Chem. Co. Inc., and used as received. Other chemicals and solvents were of analytical grade and obtained from commercial sources.

General Procedure for Synthesis of ^{11}C-*Labelled Ketones.*— [^{11}C]Carbon monoxide was trapped, at room temperature, in a 3 cm^3 septum-equipped vial containing the halide (15 μmol), $Pd(PPh_3)_4$ (0.6 mg, 0.5 μmol) and solvent (300 mm^3). After trapping, the organotin reagent (15 μmol) was added and the reaction vessel was heated at 90 °C for 4 min. The radiochemical yield and the product identity was determined by analytical HPLC (Beckman Ultrasphere C-18 5 μm or Spherisorb ODS 5 μm column, 250 × 4.6 mm) (**1**–**3**) and by GLC (J&W Scientific DB-WAX capillary column, 30 m × 0.25 mm) (**3**). In some experiments the labelled product was purified by semi-preparative HPLC using a Beckman Ultrasphere C-18 5 μm column (250 × 10 mm), isocratic elution 5 cm^3 min^{-1} with 95:5 (**1**), 45:55 (**2**) or 25:75 (**3**) of 0.05 mol dm^{-3} ammonium formate (pH 3.5) in acetonitrile–water (50:7). The fraction containing product **1**, **2** or **3** was collected at approximately 4, 7 or 9 min, respectively.

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