Rapid Mild Syntheses of [11C]Benzophenones by Pd(0)-Catalysed 11C-Carbonylative Coupling of Iodoarenes with Phenyltributylstannane in DME-Water

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Palladium(0)-catalysed ^{11}C-carbonylative coupling of iodoarenes (RC_6H_4I; R = H, 2-Me, 3-Me, 4-F, and 4-CF$_3$) with phenyltributylstannane for 1 min in 1,2-dimethoxyethane-water (4: 1 v/v) at room temperature gave [11C]benzophenones ($RC_6H_4{}^{11}COPh$) in high radiochemical yields (58–82%, decay-corrected from trapped [11C]carbon monoxide). The efficiency of [11C]carbon monoxide trapping from a single pass into the reaction medium was 4.5–6.2%. The reaction conditions are suitable for the rapid, efficient introduction of cyclotron-produced carbon-11 ($t_{1/2}$ = 20.3 min) into substituted benzophenones as prospective labelling agents and radiopharmaceuticals for application in medical imaging with positron emission tomography.

INTRODUCTION

Positron emission tomography (PET) is a powerful molecular imaging modality in clinical research (1–4) and in drug discovery and development (5). PET is also increasingly used for clinical diagnosis (6). The power of PET stems from the

specificity of the radiotracers and radioligands that are used to report biochemical or physiological information. The further development of PET will partly depend on an increasing availability of versatile radiochemistry for labelling new and established radiopharmaceuticals with positron-emitters, such as carbon-11. Carbon-11 is short-lived ($t_{1/2}$ = 20.3 min) and therefore radiochemistry has to be fast and efficient, starting with easily accessible cyclotron-produced materials, such as [^{11}C]carbon dioxide (7). Versatile, rapid and efficient methods for labelling benzophenones with carbon-11 would be useful in providing new labelling agents and radiopharmaceuticals. Only a few procedures have been used to prepare [^{11}C]benzophenones (8–16). The most promising methods are based on palladium(0)-catalysed carbonylations with [^{11}C]carbon monoxide (9–16), with the latter generated by efficient reduction of cyclotron-produced [^{11}C]carbon dioxide on heated zinc (17), molybdenum (14) or activated charcoal (17).

Recently, we have reported a very rapid and mild route to high radiochemical yields of [^{11}C]benzophenones, based on [^{11}C]carbonylative coupling of diaryliodonium salts with organostannanes in 1,2-dimethoxyethane (DME)-water at room temperature (15, 16). Here we report that the use of aryl iodides in place of the iodonium salts, under virtually the same reaction conditions, is a similarly effective route to [^{11}C]benzophenones.

RESULTS AND DISCUSSION

In view of our previous success in using a DME-water medium for the preparation of [^{11}C]benzophenones by ^{11}C-carbonylative coupling of diaryliodonium salts with organostannanes (15, 16), we were interested to see if this medium would also be effective for the [^{11}C]carbonylative coupling of aryl iodides with organostannanes, and how the results would compare with those reported for a similar reaction in other solvents (9–12). We first performed control reactions with non-radioactive carbon monoxide. Carbonylation of iodobenzene plus phenyltributylstannane in DME-water (4: 1 v/v) in the presence of palladium(II) chloride at room temperature for 1 min gave benzophenone as the main product. In reactions run up to 30 min in the absence of palladium(II) catalyst, an unknown product, comigrating with benzaldehyde in the HPLC analysis, was produced in low yield, but no benzophenone. This clearly demonstrated the important role of palladium(II) in the carbonylative coupling. The synthesis of [^{11}C]benzophenone was then undertaken to examine further the role of the reactants and to establish general reaction conditions.

[¹¹C]Carbon monoxide was readily produced from the 'on-line' reduction of cyclotron-produced [¹¹C]carbon dioxide over activated charcoal at 900°C (17). This product was collected in nitrogen (40 ml) and was shown to be free of residual [¹¹C]carbon dioxide. The procedure converts oxygen in the irradiated target gas into carbon monoxide, and hence the [¹¹C]carbon monoxide is 'carrier-added'. However, the amount of carrier per batch is small (~ 2 μmol).

Several control reactions were run with [¹¹C]carbon monoxide. ¹¹C-Carbonylation of iodobenzene alone in DME-water (4: 1 v/v) gave a quantitative yield of a radioactive product having the same retention time in the HPLC analysis as benzaldehyde[1] (Table 1, entry 1), in accord with the finding from the experiment performed with non-radioactive carbon monoxide. This product is presumably formed *via* direct insertion of carbon monoxide into the carbon-iodine bond:

$$PhI + ^{11}CO \rightarrow Ph^{11}COI$$
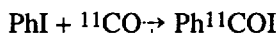
Transformation of such an intermediate into [¹¹C]benzaldehyde would require a source of hydrogen or 'hydride', such as sodium formate (18) or trimethyltin hydride (19, 20), which would almost certainly not have been available in the reaction medium. Hence, the identity of this radioactive product ([¹¹C]unknown A) remains uncertain.

Table 1. Radiochemical yields of products from various ¹¹C-carbonylation reactions performed in DME-water (4: 1 v/v; 0.4 ml) at RT for 1 min.

Entry	PhI	PhSnBu₃	PdCl₂	Radiochemical yield[a]		
				(Ph)₂¹¹CO	Ph¹¹CO₂H	[¹¹C]Unknown A
	(μmol)	(μmol)	(μmol)	(%)	(%)	(%)
1	2.46	0	0	0	0	100
2	2.46	0	0.025	0	93	7
3	0	2.46	0	0	0	>75[b]
4	0	2.46	0.013	40	< 5	55
5	2.46	2.46	0	0	2	98
6	2.46	2.46	0.025	82	0	18
7	9.83	10.1	0.10	98[c]	0	0

[a] Decay-corrected radiochemical yield by radio-HPLC analysis. [b] The other radioactive product was [¹¹C]unknown B. [c] The reaction was performed for 20 min.

[1]N.B. All cited radiochemical yields are decay-corrected from trapped [¹¹C]carbon monoxide.

The same reaction, performed in the presence of palladium(II), produced [11C]benzoic acid in 93% radiochemical yield (Table 1, entry 2). [11C]Unknown A was the minor radioactive byproduct. [11C]Benzoic acid is almost certainly formed by oxidative addition of palladium(0) to iodobenzene, followed by carbon monoxide insertion to give a σ-aryl-palladium complex that then reacts with water (Figure 1) (21).
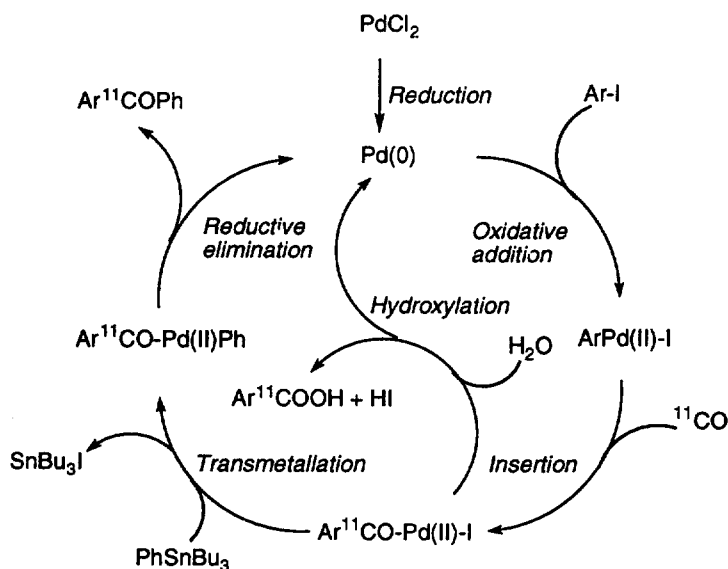

Figure 1. The probable catalytic cycle for the 11C-carbonylative coupling of iodoarenes with phenyltributylstannane to give [11C]benzophenones, showing the competitive production of [11C]benzoic acid.

11C-Carbonylation of phenyltributylstannane alone gave a high radiochemical yield of [11C]unknown A plus another radioactive compound ([11C]unknown B), which eluted as a shoulder to the main radioactive peak in the HPLC analysis (Table 1, entry 3). When the same experiment was repeated in the presence of palladium(II) chloride, [11C]unknown A was the main radioactive product, but [11C]benzophenone was also produced in high radiochemical yield, with [11C]benzoic acid as a low level byproduct (Table 1, entry 4). This shows that [11C]carbon monoxide can react directly with phenyltributylstannane.

11C-Carbonylation of a mixture of phenyltributylstannane and iodobenzene, in the absence of palladium(II), gave a very high radiochemical yield of [11C]unknown A (98%), a trace of [11C]benzoic acid, but no [11C]benzophenone (Table 1, entry 5).

[^{11}C]Benzophenone was obtained in 82% radiochemical yield when the iodobenzene and phenyltributylstannane were in equimolar ratio, for palladium(0)-catalysed ^{11}C-carbonylation (Table 1, entry 6). The radiochemical yield increased to 98% when the concentration of reactants was increased almost 4-fold and the reaction time was extended to 20 min (Table 1, entry 7). These findings fit with the generally accepted path (22–24) for the palladium(0)-catalysed carbonylative syntheses of aryl ketones (25, 26) from aryl iodides and organometallic reagents. In the catalytic cycle[2], there is first oxidative addition of palladium(0)[3] to the iodoarene to give a σ-aryl-palladium(II) complex followed by [^{11}C]carbon monoxide insertion and finally transmetallation with the organostannane, releasing the aryl ketone and palladium(0) (Figure 1).

The increase in decay-corrected radiochemical yield of [^{11}C]benzophenone from 83 to 98% on extending the reaction time from 1 to 20 min has no practical advantage, because of radioactive decay *i.e.* the non-decay-corrected radiochemical yields are 80 and 49.5%, for 1 and 20 min reaction times, respectively. This yield is almost that achieved *via* ^{11}C-carbonylative coupling of iodonium salts with phenytributylstannane under the same conditions (96%) (15, 16), and is either similar or superior to those reported (9–12, 14) for various other palladium(0)-catalysed ^{11}C-carbonylative couplings of iodobenzene with organometallic reagents under harsher conditions (Table 2).

Table 2. Radiochemical yields of [^{11}C]benzophenone obtained from various Pd(0)-catalysed ^{11}C-carbonylative couplings of iodobenzene with organometallic reagents.

PhI	ArMX$_n$	Pd	Solvent	Temp.	Time	Yield[a]	Reference
(µmol)				(°C)	(min)	(%)	
45–85	45–85[b]	1.4[e]	NMP	130	5	60–69	11,12
15	15[b]	0.5[f]	DMSO	90	4	82	9,10
94	82[c]	3.2[g]	DMSO	100	5	69	14
2.46	2.46[d]	0.025[h]	DME-water (4: 1 v/v)	RT	1	83	This work

[a] Decay-corrected radiochemical yield by radio-HPLC analysis. [b] PhSnMe$_3$. [c] PhB(OH)$_2$. [d] PhSnBu$_3$. [e] Pd(dppf)$_4$. [f] Pd(PPh$_3$)$_4$. [g] Pd(PPh$_3$)$_2$Cl$_2$. [h] PdCl$_2$.

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[2]Since the reactions are estimated to contain 0.10 µmol of carrier carbon monoxide and 0.025 µmol of PdCl$_2$, the catalytic cycle would need to turn over only a small number of times.

[3]The added palladium(II) is readily reduced to palladium(0) for entry into the catalytic cycle.

The most practical conditions found for the production of [11C]benzophenone from iodobenzene (Table 1, entry 6) were also applied to substituted iodoarenes (1-fluoro-4-iodobenzene, 4-iodobenzotrifluoride, 2-iodotoluene and 3-iodotoluene) and gave the expected substituted [11C]benzophenones in high radiochemical yields (58–78%) (Table 3). These results confirm that the procedure is tolerant of electron-donating or electron-withdrawing substituents in the aryl iodide. Though, we have obtained even higher radiochemical yields of some of these [11C]benzophenones (RPh11COPh; R = 3-Me, 4-CF$_3$, 4-F) by 11C-carbonylative coupling of diphenyliodonium bromide with substituted phenyltributylstannane (15, 16), this procedure will be generally useful in view of the wide availability of substituted iodoarenes.

In all cases using substituted iodobenzenes, [11C]unknown A (17–37%) and [11C]benzophenone (< 5%) were produced as radioactive byproducts (Table 3). The observed [11C]benzophenone must arise from the coupling of two phenyltributylstannane molecules, as observed in the control experiment omitting aryl iodide (Table 1, entry 4). It is evident that when phenyltributylstannane is present in the reaction mixtures [11C]benzoic acid is a minor byproduct, if formed at all (Tables 1 and 3). This indicates that transmetallation of the σ-aryl-palladium(II) complex, Ar11COPd(II)I, is more rapid than its competing hydroxylation (Figure 1). Under the conditions described here, transmetallation must proceed at a fast rate, even though it is likely to be rate-limiting (22–24). It may be expected that the use of substituted phenyltributylstannanes with substituted aryl iodides will lead to [11C]benzophenones bearing substituents in each ring, though this has yet to be tested.

Table 3. Radiochemical yields of [11C]benzophenones and other byproducts from Pd(0)-catalysed 11C-carbonylation reactions.

Entry	ArI	Radiochemical yield[a]		
		Ar11COPh (%)	Ph11CO$_2$H (%)	[11C]Unknown A (%)
1	2Me-C$_6$H$_4$I	61	< 5	34
2	3Me-C$_6$H$_4$I	69	< 5	26
3	4F-C$_6$H$_4$I	78	< 5	17
4	4CF$_3$-C$_6$H$_4$I	58	< 5	37

[a] Decay-corrected radiochemical yield by radio-HPLC analysis.

Carbon monoxide has a low solubility in most organic solvents. We found that on single pass of [11C]carbon monoxide into the DME-water reaction media that 4.5–6.2% of the radioactivity became trapped in solution. Low trapping efficiency has been observed by others for other solvent systems (9, 10). Efficient utilisation of the available [11C]carbon monoxide can be achieved by different means, for example by recirculation of the untrapped gas (11, 12) or by the use of a high pressure miniature autoclave (27).

Clearly, our results, when taken with those of other workers (10), show that the choice of solvent is critical not only for the adequate entrapment of the [11C]carbon monoxide but also for its reactivity in the palladium(0)-catalysed 11C-carbonylation procedure. This suggests that some solvents participate in the reaction cycle, for example by coordinating to palladium. In this regard, the presence of water is known to improve selectivity and yield in some palladium(0)-catalysed coupling reactions of organostannanes (28). In previous studies of palladium(0)-catalysed 11C-carbonylation reactions, it was found that polar solvents, such as *N*-methylpiperidin-2-one (NMP) and dimethyl sulfoxide (DMSO), gave higher radiochemical yields than ethers, such as tetrahydrofuran and 1,3-dioxane (10). However, in DMSO more byproduct was formed than in NMP (12). Our finding that the use of a moderately polar DME-water mixture as solvent gives higher radiochemical yields of [11C]benzophenones under milder conditions seems to fit with the previously observed pattern of solvent effects. The protic nature of DME-water seems to be beneficial rather than detrimental. Further investigation is needed to fully understand these solvent effects, so that they may be exploited for maximal product selectivity and yield.

CONCLUSION

The results affirm that palladium(0)-catalysed 11C-carbonylative coupling of iodoarenes with phenyltributylstannane is an effective general route to [11C]benzophenones, and that this process is susceptible to useful solvent effects. Use of DME-water (4: 1 v/v) as solvent under mild conditions gave [11C]benzophenone in higher radiochemical yield than reported for reactions in other solvents under harsher conditions.

EXPERIMENTAL

Materials

Benzaldehyde, benzoic acid, aryl iodides and reference benzophenones were purchased from Lancaster Synthesis. Phenyltributylstannane, palladium(II) chloride and all other reagents and were purchased from Aldrich Chemical Co. They were of greater than 99.5% purity and were used without further purification.

General Analytical Methods

Radio-GC was performed using a Shimadzu, GC 14A instrument, fitted with a Poraplot 007 column (25 m, 25°C) connected to a capillary column injector (25°C) supplied with helium as carrier gas (1.5 bar; flow rate 5 ml/min). The output was connected to a micro-thermal conductivity detector connected in series to a custom-built radioactivity detector. Retention times (min): carbon dioxide (1.4); carbon monoxide (1.85).

Radio-HPLC was performed using a Waters µ-Bondapak™ C18 column (300 x 7.8 mm o.d.) eluted with acetonitrile-water-triethylamine (60: 40: 0.25 by vol.) at 3 ml/min. Radioactive peaks were identified by co-injection of reference compounds that were detected by their absorbance at 254 nm. Retention times (min): benzoic acid (2.20); benzaldehyde (5.5); benzophenone (8.8); 4-fluoro-benzophenone (9.5); 2-methyl-benzophenone (10.0); 3-methyl-benzophenone (10.7); 4-trifluorobenzophenone (13.5).

Production of [^{11}C]carbon monoxide

[^{11}C]Carbon dioxide was produced from the $^{14}N(p,\alpha)^{11}C$ nuclear reaction by irradiation of a target of nitrogen-0.1% oxygen (15 bar) with protons (19 MeV). The [^{11}C]carbon dioxide was transferred in nitrogen from the target to a lead-shielded 'hot-cell' through stainless steel tubing (1.8 in o.d.) at 500 ml/min. A portion of this gas was directed through a heated quartz tube containing charcoal at 900°C (17). The generated [^{11}C]carbon monoxide was passed over a sodalime trap to eliminate any traces of unconverted [^{11}C]carbon dioxide and collected in a nitrogen-flushed 50 ml syringe as a mixture with nitrogen gas. The radiochemical purity of the [^{11}C]carbon monoxide was > 99% by radio-GC analysis.

Control (non-radioactive) carbonylation reactions

Phenyltributylstannane (5.6 μmol) was dissolved in DME-water (4: 1 v/v; 0.4 ml) and iodobenzene (2.46 μmol) added with stirring. Carbon monoxide was bubbled through the reaction mixture. Reaction was allowed to proceed at room temperature. The reaction mixture was sampled at 5, 10, 15, 20, 25 and 30 min for HPLC analysis. The reaction was repeated in the presence of palladium(II) chloride (0.025 μmol), and the reaction mixture analysed at 1 min by HPLC.

General procedure for synthesis of [¹¹C]benzophenones

Iodobenzene or a substituted analogue (2.46 μmol) and phenyltributylstannane (2.46 μmol) were dissolved in DME-water (4: 1 v/v; 0.4 ml) within a septum-sealed reaction vial (Pierce, volume, 2.0 ml). Palladium(II) chloride (0.025 μmol) in DME-water (4: 1 v/v; 19 μl) was added, except where stated (see Table 1), before a known quantity of radioactive [¹¹C]carbon monoxide (110–220 MBq; 3–6 mCi) in nitrogen was passed from a 50 ml glass syringe *via* a stainless steel needle (40 mm; 21 gauge) into the vented solution over ~ 30 s. The sealed reaction mixture was left to stir at room temperature for 1 min. The radioactivity trapped in the reaction vial was measured. The reaction mixture was promptly analysed by radio-HPLC.

Control ¹¹C-carbonylation reactions

Control ¹¹C-carbonylation reactions were performed in which various reaction components of the general procedure were omitted or altered in quantity (Table 1).

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