Palladium(II)-mediated ^{11}C-carbonylative coupling of diaryliodonium salts with organostannanes—a new, mild and rapid synthesis of aryl [^{11}C]ketones

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Palladium(II)-mediated [^{11}C]carbonylative coupling of diaryliodonium salts with aryltributylstannanes for 1 min in DME–water (4:1 v/v) at RT gives a new mild and rapid route to aryl [^{11}C]ketones. Substituted aryltributylstannanes couple with diphenyliodonium bromide to give substituted [^{11}C]benzophenones in generally very high radiochemical yield (>98%, decay-corrected), while diphenyliodonium tosylates, bearing one or two substituents in one ring, couple with phenyltributylstannane to give a mixture of substituted (30–43%) and unsubstituted [^{11}C]benzophenone (47–66%). These reactions are highly attractive for introducing cyclotron-produced carbon-11 ($t_{1/2}$ = 20.4 min) into prospective radiotracers for application in medical imaging with positron emission tomography.

Introduction

Carbon-11 ($t_{1/2}$ = 20.4 min; β^+ = 100%) is especially useful for labelling compounds as radiopharmaceuticals for medical imaging with positron emission tomography (PET).[1] The increasingly widespread application and development of PET stimulates a need for rapid and efficient methods for the site-specific incorporation of carbon-11 into prospective radiopharmaceuticals. Carbon monoxide has a rich chemistry for the introduction of carbonyl groups into organic compounds.[2] Although [^{11}C]carbon monoxide is readily prepared from cyclotron-produced no-carrier-added [^{11}C]carbon dioxide,[3,4] it has not yet found widespread use for labelling organic compounds. One of the reasons is the low solubility of [^{11}C]carbon monoxide in organic solvents, which limits the efficiency with which it can be trapped by a single pass into a reagent solution. However, there are now methods to overcome this problem, including rapid recirculation of untrapped [^{11}C]carbon monoxide through the reagent solution[5] or confinement of the [^{11}C]carbon monoxide with reactants in a high pressure microautoclave.[6] Renewed interest in the potential to apply [^{11}C]-carbon monoxide to the solution of labelling problems is therefore warranted.

It has recently been reported that diaryliodonium salts ($Ar^1I^+Ar^2X^-$) † couple carbonylatively with organostannanes in the presence of a palladium(II) catalyst to give ketones.[7b] Since we have a ready access to several new diaryliodonium salts[8,9] and to [^{11}C]carbon monoxide, we were interested to see if this reaction could be applied generally to the rapid preparation of [^{11}C]ketones (Scheme 1). Here we report our findings on the preparation of substituted [^{11}C]benzophenones from various diaryliodonium salts and aryltributylstannanes.

Results and discussion

[^{11}C]Carbon monoxide was readily produced by reducing cyclotron-produced no-carrier-added [^{11}C]carbon dioxide over charcoal at 900 °C.[3] On average about 6.0% (4.5–7.5%; n = 56) of the radioactivity was trapped by a single pass of the nitrogen–[^{11}C]carbon monoxide through the small volume (~0.4 ml) of solvent (DME–water; 4:1 v/v)[7] in the presence of reactants. No effect of solvent on trapping efficiency was studied here. However, polar solvents, such as DMSO, trap [^{11}C]carbon monoxide more efficiently than THF.[5,6] By switching to another more polar solvent, some advantage might have been gained for [^{11}C]carbon monoxide solubilisation, but perhaps at the expense of reactivity.[10]

Palladium(II)-mediated ^{11}C-carbonylative coupling of diphenyliodonium iodide (**1a**) with phenyltributylstannane (**2a**) at room temperature for 1 min gave a high radiochemical yield ‡ of [^{11}C]benzophenone (**3a**) (55–75%, average 65% for n = 5, decay-corrected). On increasing the reaction time to 5, 10 and 20 min, the decay-corrected radiochemical yield increased marginally to 75, 80 and 80%, respectively. Hence, a 1 min reaction time gave the highest practical (non-decay-corrected) radiochemical yield. The main radioactive byproduct in all these reactions was [^{11}C]benzoic acid. This product was also obtained in a control reaction from which phenyltributylstannane was omitted. [^{11}C]Benzaldehyde was observed as another minor byproduct in the reactions conducted for 1 min (5–11%). This product was also obtained in a control reaction (1 min) from which palladium(II) was omitted.

In reactions performed at room temperature for 20 min, the radiochemical yield of [^{11}C]benzophenone increased with the molar ratio of phenyltributylstannane to diphenyliodonium iodide and was highest for a ratio of 2 (Fig. 1). By analogy with the reaction course generally accepted for other palladium(II)-mediated carbonylation reactions,[11] it is assumed that the [^{11}C]carbonylative coupling of iodonium salts with aryltributylstannanes proceeds through a catalytic cycle, involving oxidative addition of palladium(0)§ to the iodonium salt to form a

† Although the structure of the iodonium salts is shown formally as $Ar^1I^+Ar^2X^-$, there is substantial evidence that these can exist as bridged dimers where X^- is halide.[7a]

‡ All radiochemical yields are decay-corrected and are based on the radioactivity initially trapped in the solvent.

§ The added palladium(II) chloride is readily reduced to palladium(0).[2]

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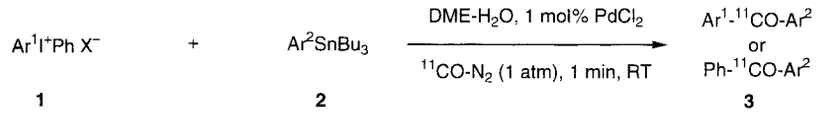


1

2

3

1a	Ar^1 = Ph	**2a**	Ar^2 = Ph	**3a**	Ar^1 = Ph	Ar^2 = Ph
1b	2-Me-C_6H_4	**2b**	2-Me-C_6H_4	**3b**	2-Me-C_6H_4 or Ph	Ph or 2-Me-C_6H_4
1c	3-Me-C_6H_4	**2c**	3-Me-C_6H_4	**3c**	3-Me-C_6H_4 or Ph	Ph or 3-Me-C_6H_4
1d	2-MeO-C_6H_4	**2d**	2-MeO-C_6H_4	**3d**	2-MeO-C_6H_4 or Ph	Ph or 2-MeO-C_6H_4
1e	4-CF_3-C_6H_4	**2e**	4-CF_3-C_6H_4	**3e**	4-CF_3-C_6H_4 or Ph	Ph or 4-CF_3-C_6H_4
1f	4-F,3-Me-C_6H_3	**2f**	3,5-diF-C_6H_3	**3f**	Ph	3,5-diF-C_6H_3
		2g	4-F-C_6H_4	**3g**	Ph	4-F-C_6H_4
				3h	4-F,3-MeC_6H_3	Ph

Scheme 1 Palladium(II)-mediated [^{11}C]carbonylative coupling of diaryliodonium salts with aryltributylstannanes. In **1a**, $X^- = I^-$, Br^-, NO_3^- or OTs^- and in **1b**–**1f**, $X^- = OTs^-$.

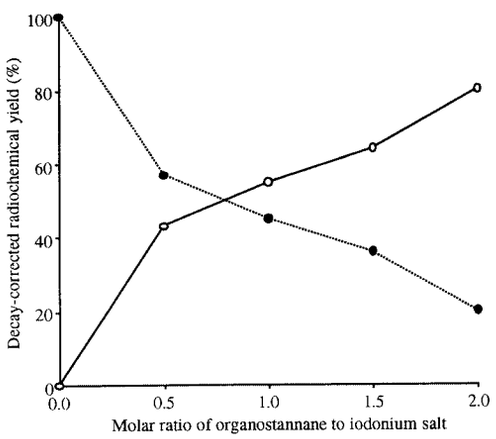


Fig. 1 Dependence of the radiochemical yield (decay-corrected) of [^{11}C]benzophenone (○) and [^{11}C]benzoic acid (●) on the ratio of phenyltributylstannane to diphenyliodonium bromide in palladium(II)-mediated ^{11}C-carbonylative coupling at RT for 20 min.

σ-arylpalladium(II) complex, [^{11}C]carbon monoxide insertion, transmetallation with the aryltributylstannane, and finally reductive elimination of palladium(0) to give the [^{11}C]ketone (Scheme 2). Hence, the transmetallation step seems to be preferred to the formation of the byproducts, [^{11}C]benzaldehyde or [^{11}C]benzoic acid, which presumably arise by abstraction of a free proton or hydroxy group, respectively, from the reaction medium. This preference is promoted by a high ratio of the phenyltributylstannane.

With respect to variation of the anion in the diphenyliodonium salt, [^{11}C]benzophenone was obtained in 75, 90, 92 and 96% radiochemical yields from the iodide, tosylate (toluene-*p*-sulfonate), nitrate and bromide, respectively. Since the bromide gave the highest radiochemical yield of [^{11}C]benzophenone with low byproduct formation, all further coupling experiments with diphenyliodonium were run with bromide as counteranion. However, there is no clear indication for the role that the anion plays in the reaction.

Two approaches were adopted for the general extension of the conditions of the reaction [RT, 1 min, 1 mol% Pd(II)] to the preparation of substituted [^{11}C]benzophenones, namely i) the use of different substituted aryltributylstannanes (**2a**–**2g**) with diphenyliodonium bromide as partner and ii) the use of different diaryliodonium tosylates bearing one or more substituents in one aryl ring (**1b**–**1f**) with phenyltributylstannane as partner.

By the use of variously substituted phenyltributylstannanes with diphenyliodonium bromide, exceptionally high radiochemical yields (~98%) of several substituted [^{11}C]benzophenones (**3c**–**3g**) were obtained (Table 1). Only the 3-methylbenzophenone (**3b**) was obtained in a substantially lower, but still useful, radiochemical yield (44%). In this case, [^{11}C]benzaldehyde and [^{11}C]benzoic acid were substantial radioactive byproducts.

When different mono-substituted diaryliodonium tosylates were used to partner phenyltributylstannane, the radiochemical yields of the expected substituted [^{11}C]benzophenones (**3b**–**3h**) were substantially lower (30–43%) than from the already described alternative approach employing a substituted aryltributylstannane (Table 2). In each of these reactions the major radioactive product was [^{11}C]benzophenone (47–51%). Clearly,

Table 1 Decay-corrected radiochemical yields of aryl [^{11}C]ketones ($Ph^{11}COAr^2$) from the reactions of diphenyliodonium bromide with different aryltributylstannanes (Ar^2SnBu_3) in the presence of palladium(II) chloride at RT for 1 min

Organostannane precursor	Ar^2	Radiochemical yield of $Ph^{11}COAr^2$ (%)[a]
2a	Ph	96 (**3a**)
2b	2-Me-C_6H_4	44[b] (**3b**)
2c	3-Me-C_6H_4	>98 (**3c**)
2d	2-OMe-C_6H_4	>98 (**3d**)
2e	4-CF_3-C_6H_4	>98 (**3e**)
2f	3,5-di-F-C_6H_3	>98 (**3f**)
2g	4-F-C_6H_4	>98 (**3g**)

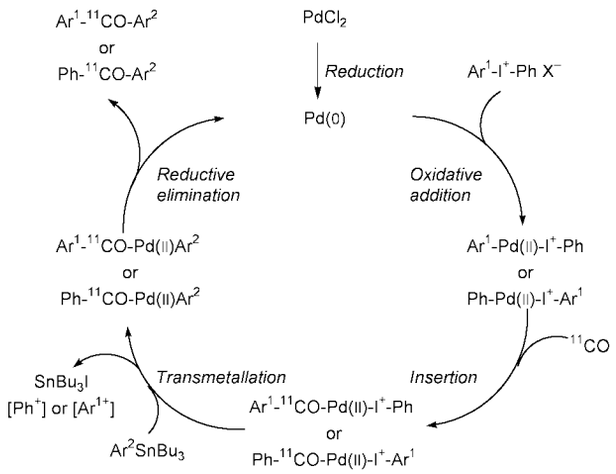
[a] Radiochemical yield (decay-corrected) from trapped [^{11}C]carbon monoxide. [b] The radioactive byproducts were [^{11}C]benzoic acid, [^{11}C]benzaldehyde and an unknown compound (aggregate radiochemical yield 56%).

Table 2 Decay-corrected radiochemical yields of aryl [^{11}C]ketones from the reaction of different diaryliodonium tosylates ($PhI^+Ar^1\ OTs^-$) with phenyltributylstannane (**2a**) in the presence of palladium(II) chloride at RT for 1 min

Iodonium salt precursor	Ar^1	Radiochemical yield (%)[a]		
		$Ph^{11}COAr^2$	$Ph^{11}COPh$	Others[b]
1b	2-Me-C_6H_4	42 (**3b**)	48	10
1c	3-Me-C_6H_4	43 (**3c**)	47	10
1d	2-OMe-C_6H_4	37 (**3d**)	62	<1
1e	4-CF_3-C_6H_4	30 (**3e**)	66	4
1f	4-F,3-Me-C_6H_3	37 (**3h**)	51	12

[a] Radiochemical yield (decay-corrected) from trapped [^{11}C]carbon monoxide. [b] [^{11}C]Benzoic acid plus [^{11}C]benzaldehyde.

this product was expected since either aryl group in the iodonium salt, phenyl or substituted phenyl, can in principle be incorporated into [^{11}C]ketone (Scheme 2). The total radiochemical yield



Scheme 2 Probable reaction cycle for the palladium(II)-mediated [^{11}C]carbonylative coupling of diaryliodonium salts with aryltributylstannanes to produce aryl [^{11}C]ketones.

of aryl [^{11}C]ketones ranged from 88 to 99% (Table 2), showing again the overall efficiency of the palladium(0)-mediated process. In the iodonium salts, aryl rings bearing strongly electron-withdrawing substituents (F or CF_3) in the *para* position or a bulky *ortho* substituent (OMe) were markedly less likely to be incorporated into the aryl [^{11}C]ketone product than a phenyl ring. This may reflect the existence of a trigonal bipyramidal transition state for the initial oxidative addition of palladium(0), centred on the iodine(III) atom, in which one aryl group is preferentially in an equatorial position and the other in an axial position, with the preference determined by the pattern of substitution, especially the presence of a bulky *ortho* substituent.[12] [^{11}C]Benzaldehyde and [^{11}C]benzoic acid were seen as low level byproducts in all the reactions. The use of an iodonium salt having identical substituents in each aryl ring would clearly be expected to give a single aryl [^{11}C]ketone product. Such salts can be prepared by several general procedures.[13–17]

The radiochemical yields of [^{11}C]ketones obtained here compare favourably with those reported from the [^{11}C]carbonylative coupling of aryl iodides with aryltrialkylstannanes[5,6,10] and are achieved under significantly milder conditions (shorter reaction time and lower temperature). They reaffirm the efficiency that can be achieved in Pd(II)-mediated [^{11}C]carbonylation reactions for the synthesis of aryl [^{11}C]ketones. This method is further attractive for application in PET radiopharmaceutical production because the reagents are stable, required in very small amounts and used in a single pot. High specific radioactivities can be expected, since the isotopic dilution of the [^{11}C]carbon monoxide with stable carbon monoxide from the atmosphere is small; indeed carrier aryl ketones were not detected by UV absorbance in the HPLC analyses of reaction mixtures. The present approach is versatile with respect to functionality in either the diaryliodonium salt or the partner aryltributylstannane. Hence, the method should be extendable to the preparation of [^{11}C]benzophenones bearing different substituents in each ring. Clearly, the opportunity that this method presents to prepare substituted [^{11}C]benzophenones in high radiochemical yield from a 1 min reaction at room temperature is highly attractive for ^{11}C-chemistry and future PET radiopharmaceutical development.

Experimental

Materials

Diphenyliodonium iodide, bromide and nitrate, reference diaryl ketones, benzoic acid and benzaldehyde were purchased from Lancaster Synthesis. Diaryliodonium tosylates were prepared, as reported.[8,9] Aryltributylstannanes were purchased from Maybridge Chemical Co., except phenyltributylstannane which was purchased from Aldrich Chemical Co. Palladium(II) chloride and all other reagents were purchased from Aldrich Chemical Co. They were of greater than 99.5% purity and 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^{-1}). The output was connected to a micro-TCD detector connected in series to a custom built radioactivity detector. Radio-HPLC was performed using a μ-Bondapak C18 column (300 × 7.8 mm od) eluted with acetonitrile–water–triethylamine (60 : 40 : 0.025 by volume) at 3 ml min^{-1}. Radioactive peaks were identified by coinjection of reference compounds that were detected by their absorbance at 254 nm.

Preparation of [^{11}C]carbon monoxide

[^{11}C]Carbon dioxide was produced from the ^{14}N(p,α)^{11}C nuclear reaction by irradiation of a target of nitrogen–0.1% oxygen (15 bar) with 19 MeV protons. The [^{11}C]carbon dioxide was transferred in nitrogen from the target to a lead-shielded 'hot-cell' through stainless steel tubing at 500 ml min^{-1} and then through a heated quartz tube containing charcoal at 900 °C.[3] 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.

General procedure for synthesis of [^{11}C]ketones

Either diphenyliodonium bromide (2.80 μmol) plus aryltributylstannane (5.6 μmol) or diaryliodonium tosylate (2.80 μmol) plus phenyltributylstannane (5.6 μmol), were dissolved in DME–H_2O (4 : 1 v/v, 0.4 ml) within a septum-sealed reaction vial (Pierce, volume, 2.0 ml). Palladium(II) chloride (0.028 μmol) in (DME–H_2O, 4 : 1 v/v; 22 μl) was added before a known quantity of [^{11}C]carbon monoxide (111–222 MBq; 3–6 mCi) in nitrogen was passed from a 50 ml glass syringe through a needle (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.

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