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Communication

Carbon-11 Acetylation

Direct and Efficient (Carbonyl)cobalt-Mediated Aryl Acetylation Using [^{11}C]Methyl Iodide

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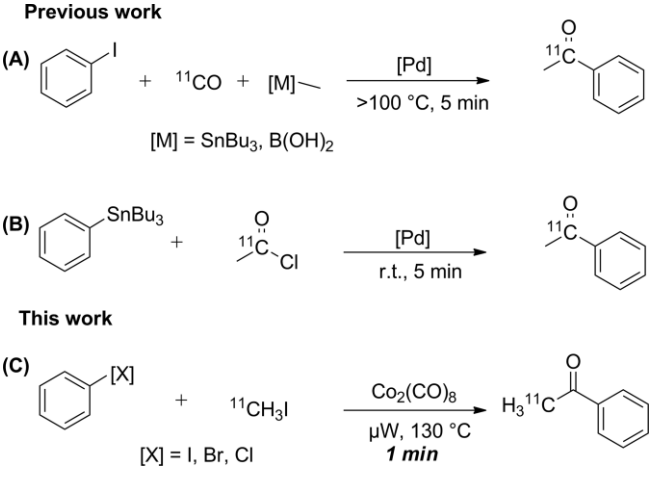
Abstract: A new strategy is reported that allows direct access to ^{11}C-labelled aryl methyl ketones by a fast and efficient (carbonyl)cobalt-mediated protocol employing [^{11}C]methyl iodide as the labelling agent. The method uses Co_2CO_8 as combined aryl halide activator and carbon monoxide source for the carbonylation reaction. The suitability of the methodology was demonstrated by the ^{11}C-labelling of a set of functionalised arenes and heteroarenes with radiochemical conversions (RCC) ranging from 22 % to 63 %.

Introduction

Positron emission tomography (PET) is a non-invasive imaging technique that uses specific probes radiolabelled with positron-emitting radionuclides to study biological processes in vivo.[1] Special synthetic procedures are required in the production of these biological probes as the radionuclides used in PET are short-lived, only present in submicromolar amounts and emit γ-radiation.[2] Carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) is an attractive radionuclide since its naturally occurring isotope, carbon-12, is present in all organic molecules. Labeling with ^{11}C can thus be achieved without altering the physicochemical or pharmacological properties of a compound. So far, the most common method for incorporation of ^{11}C is by heteroatom ^{11}C-methylation using [^{11}C]methyl iodide[3] ($^{11}CH_3I$) or [^{11}C]methyl triflate.[4]

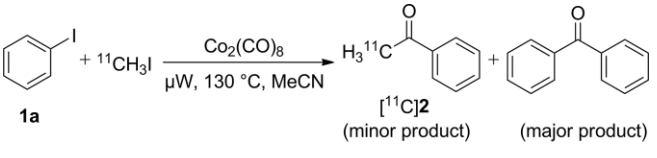
Aryl methyl ketones belong to a valuable class of carbonyl derivatives, which can serve as versatile synthetic building blocks to pharmacologically active molecules, e.g., estrone derivatives.[5] In PET radiochemistry, ^{11}C-labelled aryl methyl ketones are readily available by palladium-mediated ^{11}C-carbonylation reactions using [^{11}C]carbon monoxide[6] [Scheme 1 (A)] or [^{11}C]acetyl chloride[7] [Scheme 1 (B)]. A drawback with both of these methodologies is that they are based on technically demanding multistejjp radiosyntheses starting from the radioactive precursor [^{11}C]carbon dioxide ($^{11}CO_2$). In addition, radioligands synthesized from $^{11}CO_2$ are usually obtained at lower specific radioactivity (SRA) compared to those obtained from $^{11}CH_3I$ originated from in-target produced [^{11}C]methane ($^{11}CH_4$).[8] High SRA is often required in neuroreceptor imaging studies to avoid saturation of the receptor system by non-radioactive carrier molecules.



Scheme 1. Routes to ^{11}C-labelled aryl methyl ketones. μW = microwaves.

Results and Discussion

Inspired by Enquist and co-workers,[9] who reported an ultrafast cobalt-catalyzed route to diaryl ketones, we herein present a novel (carbonyl)cobalt-mediated protocol to form ^{11}C-labelled aryl methyl ketones using the well-established radioactive precursor $^{11}CH_3I$ [Scheme 1 (C)]. Although, the diaryl ketone remains the main product from the reaction, by exploiting the large excess of aryl halide to $^{11}CH_3I$, a sufficient amount of the desired ^{11}C-labelled aryl methyl ketone product could thereby be generated (Scheme 2).



Scheme 2. Competing diaryl ketone formation reaction. μW = microwaves.

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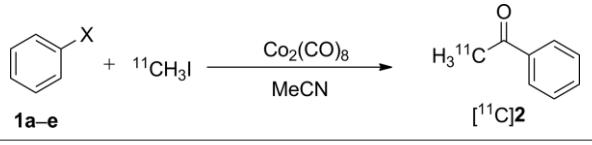
Our initial focus was to establish the preferred reaction conditions for the ^{11}C-acetylation reaction. The synthesis of [^{11}C]-acetophenone ([^{11}C]**2**) was selected as target reaction, a compound prepared by direct coupling of aryl halides **1** and $^{11}CH_3I$ using a (carbonyl)cobalt-mediated [$Co_2(CO)_8$] protocol in anhydrous acetonitrile (MeCN; Table 1), where $Co_2(CO)_8$ is acting as a combined aryl-I activator and carbon monoxide source. The reaction was performed by delivering $^{11}CH_3I$ through a solution of **1** dissolved in MeCN at room temperature (r.t.). The solution was thereafter transferred to a second vial (4 mL) pre-charged with the $Co_2(CO)_8$ located in a single-mode microwave cavity. The resultant mixture was allowed to react at 130 °C for 1 min, after which the crude reaction mixture was quenched and cooled to room temperature using compressed air. The radiochemical conversion (RCC) of the crude reaction mixture and product identity was confirmed by co-injection of a non-radioactive reference standard using radio-analytical high-performance liquid chromatography (HPLC).

Table 1. Optimization of the direct ^{11}C-acetylation of aryl halides **1a–e** with $^{11}CH_3I$.[a]



1a–e [^{11}C]**2**

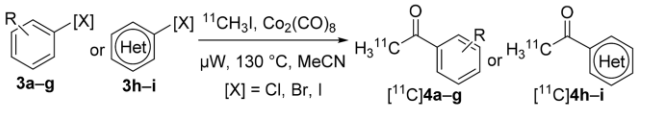
Entry	Substrate (**1a–e**)	*T* [°C]	RCC [%][b]
1	iodobenzene	130	47
2	iodobenzene	100	54
3[c]	iodobenzene	100	40
4	bromobenzene	130	62
5	chlorobenzene	130	63 ± 2[d]
6	phenyl triflate	130	16
7	fluorobenzene	130	0
8[e]	chlorobenzene	130	50
9[f]	chlorobenzene	130	54
10[g]	chlorobenzene	130	63
11	chlorobenzene	140	61
12	chlorobenzene	120	58

[a] Reaction conditions: Substrate (20 μmol), $Co_2(CO)_8$ (100 μmol), MeCN (1 mL), microwave heating. [b] Determined by radio-HPLC. [c] Thermal heating. [d] Average of two runs. [e] Substrate (10 μmol). [f] $Co_2(CO)_8$ (50 μmol). [g] $Co_2(CO)_8$ (200 μmol).

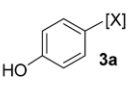
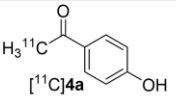
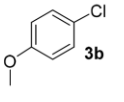
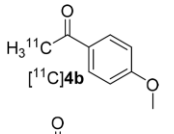
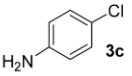
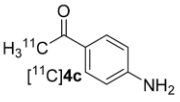
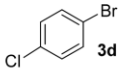
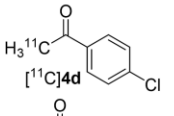
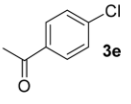
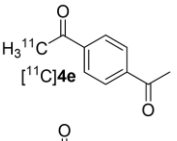
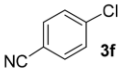
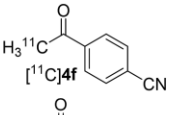
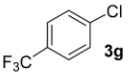
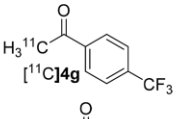
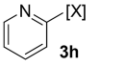
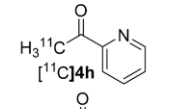
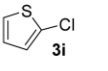
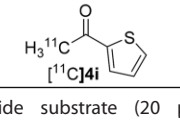
Next, a series of experiments was conducted in which the RCC of [^{11}C]MeI was investigated as a function of substrate type, temperature, and chemical amounts. Initial experiments with iodobenzene (**1a**) as substrate using microwave heating (130 °C) produced [^{11}C]**2** in a 47 % RCC (Table 1, Entry 1). Interestingly, when the temperature was decreased to 100 °C an improved RCC (54 %) was observed. This phenomenon may be explained by rapid **1a** consumption, owing to the highly rapid competing diaryl formation reaction (Scheme 2).[9] In support of this hypothesis, the less reactive aryl halides, bromobenzene and chlorobenzene, generated the desired product in good and reproducible yields, 62 % and 63 ± 2 %, respectively (Table 1, Entries 4 and 5). However, when the reaction was carried out using thermal heating a decrease in RCC was observed (Table 1, Entry 3). Fluorobenzene and phenyl triflate were found to be inefficient as substrates for the reaction (Table 1, Entries 6 and 7), and attempts to further improve the RCC by varying reagent concentration and temperature were ineffective (Table 1, Entries 8–12).

The best identified conditions (Table 1, Entry 5) were subsequently applied in the radiosynthesis of a variety of functionalized aryl methyl ketones. The results are summarized in Table 2. Aryl chlorides with electron-withdrawing groups in *para* position gave good RCCs (Table 2, Entries 4–7), whereas electron-donating groups were more or less tolerated using these conditions (Table 2, Entries 1–3). For example, electron-deficient aryl substrates, like 4-chlorobenzonitrile and 4-chlorobenzotrifluoride, provided the corresponding aryl methyl ketones in a 58–59 % RCC, whereas the electron-rich 4-chlorophenol only provided a trace amount of the desired product. On the other hand, a moderate RCC was observed for [^{11}C]4-hydroxyacetophenone when 4-iodophenol was used as substrate (Table 2,

Table 2. Direct ^{11}C-acetylation of aryl halides **3a–i** with $^{11}CH_3I$.[a] μW =microwaves.



3a–g **3h–i** [^{11}C]**4a–g** [^{11}C]**4h–i**

Entry	Aryl halide	Product	RCC [%][b,c]
1	 **3a**	 [^{11}C]**4a**	<1 23±1[d]
2	 **3b**	 [^{11}C]**4b**	47±2
3	 **3c**	 [^{11}C]**4c**	46±1
4	 **3d**	 [^{11}C]**4d**	41±1
5	 **3e**	 [^{11}C]**4e**	49±2
6	 **3f**	 [^{11}C]**4f**	59±1
7	 **3g**	 [^{11}C]**4g**	58±1
8	 **3h**	 [^{11}C]**4h**	16±2 22±1[e] 17±1[d]
9	 **3i**	 [^{11}C]**4i**	31±2

[a] Reaction conditions: aryl chloride substrate (20 μmol), $Co_2(CO)_8$ (100 μmol), MeCN (1 mL), microwave heating. [b] Determined by radio-HPLC. [c] Average of two runs. [d] Aryl iodide substrate (20 μmol). [e] Aryl bromide substrate (20 μmol).

Entry 1). The scope of the methodology was further investigated on heteroarenes. The ^{11}C-acetylation of 2-chlorothiophene resulted in a 31 % RCC into the desired aryl methyl ketone product (Table 2, Entry 9). Interestingly, RCCs of the same magnitude, 16–22 %, were observed for the formation of [^{11}C]2-acetylpyridine independently of the halide substrate being used (Table 2, Entry 8).

Finally, [^{11}C]**2** was prepared on a preparative scale. 1500 MBq (40.4 mCi) isolated product [^{11}C]**2** was obtained in a 43 decay-corrected radiochemical yield (RCY) calculated from $^{11}CH_3I$ delivered to the reaction vessel. The RCP was higher than 99 %, and the specific radioactivity was 230 GBq μmol^{-1} (6212 Ci mmol^{-1}). The reported specific radioactivity is on a similar magnitude as other ^{11}C-radioligands labelled using $^{11}CH_3I$ in our laboratory. The product identity was confirmed by co-elution on HPLC with UV and radioactive detection. However, there was a discrepancy between the obtained RCY and the previously measured analytical RCC (Table 1, Entry 5). This discrepancy could be predominantly attributed to losses during isolation of the product (e.g. at the injection to the HPLC, on the column and during collection). In addition, about 10 % of the radioactivity remained in the head-space at the end of the reaction.

Conclusions

A novel (carbonyl)cobalt-mediated, and microwave-assisted, carbonylative protocol was developed for the preparation of ^{11}C-labelled aryl methyl ketones using $^{11}CH_3I$ as the labelling agent. The reaction provides a fast and simplified route to ^{11}C-labelled aryl and heteroaryl methyl ketones.

Experimental Section

No-carrier-added $^{11}CH_4$ production was performed using a PET cyclotron, followed by previously described gas-phase conversion of $^{11}CH_4$ to $^{11}CH_3I$.[3c] The produced $^{11}CH_3I$ was trapped in vial containing aryl halide dissolved in anhydrous acetonitrile (1 mL). After complete $^{11}CH_3I$ entrapment, the solution was further transferred to a second vial equipped with a rubber septum, pre-charged with Co_2CO_8. The sealed reaction vessel was heated using a microwave cavity at the desired temperature for 1 min with active cooling, after which the vial was cooled to room temperature. The crude reaction mixture was diluted with the mobile phase (acetonitrile/water, 1:1), and the radiochemical conversion (RCC) was established with radio-HPLC.

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Keywords: Radiochemistry · Carbon-11 · Positron emission tomography · Carbonylation · Cobalt · Carbonyl ligands

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