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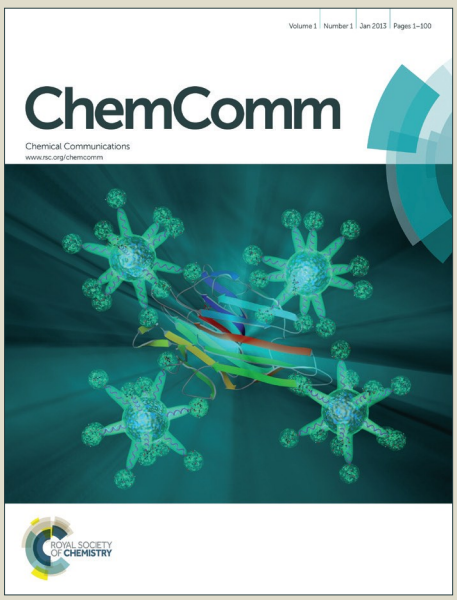

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$[^{11}C]CO_2$ to $[^{11}C]CO$ Conversion Mediated by $[^{11}C]$Silanes: A Novel Route for $[^{11}C]$Carbonylation Reactions

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A novel chemical methodology is described for the conversion of $[^{11}C]CO_2$ to $[^{11}C]CO$. Diphenylmethyl silanes trap $[^{11}C]CO_2$ and release $[^{11}C]CO$ rapidly when triggered by TBAF. Released $[^{11}C]CO$ was used to produce $[^{11}C]$*N*-benzylbenzamide and AMPA receptor ligand, $[^{11}C]$CX546, in radiochemical yields >90% within 6 min from $[^{11}C]CO_2$ production.

Carbon monoxide (CO) is a suitable carbonylating agent for the synthesis of molecules bearing a carbonyl functional group, such as carboxylic acids, carbamates, aldehydes, amides, esters, ketones and ureas.[1,2] The incorporation of CO into organic molecules generally requires harsh conditions, such as high pressure, high temperature, long reaction times and a catalyst.[1,3] Despite these requirements and the inherent toxicity of CO, it is still widely used for the synthesis of many functionalised molecules.[1,3]

CO can be produced by the reduction of carbon dioxide (CO_2)[4] using electrochemical,[5] photochemical[6], thermal[7] or chemical methods.[8-11] The chemical conversion of CO_2 into CO relies on the ability of specific molecules to form a complex with CO_2. These complexes release CO *via* an internal molecular rearrangement under specific reaction conditions. Examples include silanecarboxylic derivatives,[10,11] heterocyclic carbenes,[12] copper-boryl and copper-silyl[8] complexes[9]: so-called CO_2–CO converting reagents. Silanecarboxylic derivatives have been shown to rapidly release CO after the addition of an activator (base or fluoride salt) or by thermal decomposition.[10,11,13] By comparison, the other CO_2–CO converting reagents have been shown to be more sluggish in releasing CO.[8-10]

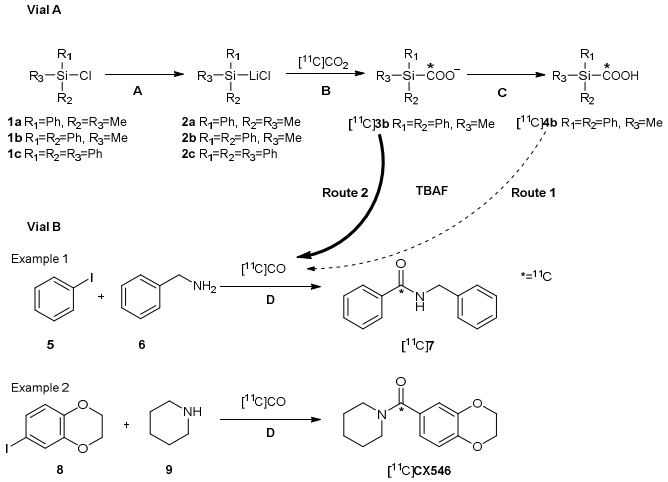
In radiochemistry, $[^{11}C]CO$ ($t_{1/2}$ = 20.4 min) carbonylation methods have been applied to the synthesis of a diverse array of $[^{11}C]$carbonyl containing molecules (tracers) and used for *in vivo* molecular imaging application with positron emission tomography (PET).[14-16] $[^{11}C]CO$ is traditionally generated by gas phase reduction of cyclotron-produced $[^{11}C]CO_2$.[17] The reduction occurs by passing $[^{11}C]CO_2$ through a heated column containing a reducing agent, such as zinc[18] or molybdenum[19]. This method requires the use of specialist equipment, a catalyst and high temperatures. Despite the demonstrated versatility of $[^{11}C]CO$ as a labelling agent, its widespread application in tracer development and *in vivo* PET imaging has been surprisingly limited.[14,15] A recent review noted that, to date, no PET tracer prepared by $[^{11}C]CO$ has yet been applied in a clinical molecular imaging study. A major reason for this is the traditional infrastructure requirement for producing $[^{11}C]CO$ from $[^{11}C]CO_2$ is only available in a few radiochemistry laboratories world-wide.[14] The development of simple and efficient methods to convert $[^{11}C]CO_2$ to $[^{11}C]CO$ using readily assembled lab-ware is therefore of great interest to the field of molecular imaging.

The aim of this work was to develop a rapid and reliable chemical conversion methodology to yield $[^{11}C]CO$ from $[^{11}C]CO_2$ *via* $[^{11}C]$silanecarboxylic derivatives and its utilisation in the synthesis of functionalised tracers using readily available lab-ware.[14]

Initially, experiments were performed to identify a silane derivative able to trap $[^{11}C]CO_2$ efficiently at 20 °C. Various silane lithium chloride derivatives bearing one, two and three, phenyl rings (**2a-c**) were synthesised from lithium and the respective silane chlorides (**1a-c**) in THF under inert atmosphere (**Fig. 1**, Vial A). Screening of

2a-c demonstrated that only **2b** trapped $[^{11}C]CO_2$ directly from the cyclotron in high efficiency (~98%) giving $[^{11}C]$**3b** with a radiochemical yield (RCY) of up to 85% (**Fig. SI1A**).

A simple two-vial setup was used to trap $[^{11}C]CO_2$ and convert it to $[^{11}C]CO$ (Vial A in **Scheme 1** and **Fig. SI2**) which was subsequently consumed in a Pd-mediated $[^{11}C]$carbonylation reaction (Vial B in **Scheme 1,** example 1) producing $[^{11}C]$*N*-benzylbenzamide ($[^{11}C]$**7**).[20] The formation of $[^{11}C]$**7** in Vial B was monitored by radio-HPLC (**Fig. 1**).



Scheme 1

Reaction conditions in Vial A: (A) **1a-c** (0.322 mmol), Li (0.864 mmol), THF (0.9 mL), 20 °C, 3 h; (B) $[^{11}C]CO_2$, 20 °C, 1 min; (C) HCl (4 M in dioxane); Route 1 and 2: TBAF 5 M in dioxane, 60 °C, 10 min. Vial B: (D) $[^{11}C]CO$, aryl halide (0.01 mmol), amine (0.46 mmol), $[(Cynnamil)PdCl]_2$ (0.007 mmol), Xantphos (0.007 mmol), THF (0.5 mL), 40 °C, 10 min.

The generation of non-radioactive CO from silanecarboxylates has been reported to be dependent on the acidification of these derivatives prior to addition of tetrabutylammonium fluoride (TBAF) (**Scheme SI1**).[11] Initial experiments used HCl to acidify $[^{11}C]$**3b** prior to addition of TBAF (2 mmol, Route 1 in **Scheme 1**). Only small amounts (2%) of $[^{11}C]CO$ was released from $[^{11}C]$**4b** at 60 °C (**Table 1, entry 1**). The effect of different TBAF equivalents and temperatures were subsequently examined. Increased $[^{11}C]CO$ release was obtained from $[^{11}C]$**4b** when a five-fold equivalents of TBAF (10 mmol) were used (**entry 2**). Changing the temperature (20 °C or 110 °C) did not improve the efficiency of $[^{11}C]CO$ release (**Table 1**, **entries 3** and **4**).

The effect of $[^{11}C]$**3b** protonation was subsequently investigated (**Scheme 1**). Surprisingly, the $[^{11}C]CO$ production (Route 2 in **Scheme 1**) increased from 4% to 25% when TBAF (10 mmol) was added at 60 °C without acidifying $[^{11}C]$**3b** prior to fluoride source addition (**Table 1**, **entries 2** and **6**). Upon TBAF addition, the complete depletion of $[^{11}C]$**3b** was observed (**Fig. SI1B**). This encouraging result suggested that the acidification of $[^{11}C]$**3b**, prior to TBAF addition, inhibited $[^{11}C]CO$ release. Consequently, the effect of different TBAF concentrations (5–80 mmol) and the time course monitoring of $[^{11}C]CO$ release were examined. The highest $[^{11}C]CO$ release was achieved with 15 mmol of TBAF at 60 °C (43%, **entry 7**). Increasing or reducing the TBAF content gave no further improvements (**entries 5**–**14**).

The time course of $[^{11}C]CO$ release from Vial A was measured by monitoring the trapping of $[^{11}C]CO$ in Vial B over time. No radioactivity transfer to Vial B was observed when heating Vial A between 20 °C and 60 °C. Subsequent addition of TBAF in Vial A caused a slight increase of radioactivity in Vial B. On purging with helium gas (for 0.5 min at 1.5 min and 4 min after TBAF addition) a complete $[^{11}C]CO$ transfer to Vial B was achieved (**Fig. SI3**, See SI for experimental details). This is consistent with the result obtained by radio-HPLC showing the complete depletion of $[^{11}C]$**3b** after TBAF addition (**Fig. SI1B)**.

Further investigations focused on increasing the RCY of $[^{11}C]$**3b** (Vial A). The preparation of **2b** under controlled inert conditions (argon glovebox) improved the RCY of $[^{11}C]$**3b** up to 85% and the $[^{11}C]CO$ release up to 51% (**entry 15**). Whereas, in the presence of double amount of **2b**, $[^{11}C]$**3b** was obtained with higher RCY (95%) but the released $[^{11}C]CO$ was very low (**entry 16**).

Radio-HPLC analysis of the reaction mixture in Vial B confirmed the production of $[^{11}C]$**7** with high RCYs of 98% (**Table 1**, **Fig. 1** and **Fig. SI4**).

In order to explore the applicability of the developed method in producing functionalised tracers, the synthesis of a selective AMPA receptor ligand, $[^{11}C]$**CX546**, was successfully achieved (**Scheme 1**, example 2). $[^{11}C]$**CX546** was produced with RCYs ≥90% after 6 min from end of cyclotron $[^{11}C]CO_2$ bombardment (EOB) (**entry 17**, **Fig. SI5**).

Table 1 Radiolabelling of $[^{11}C]$7 and $[^{11}C]$CX546 *via* $[^{11}C]$silane derivatives.

Entry	TBAF (mmol)	T (°C)	Radioactivity in Vial B (%)[f]	RCY of $[^{11}C]$7 (%)[g]	RCY of $[^{11}C]$CX546 (%)[g]
1[a,c]	2	60	2	95	
2[a,c]	10	60	4	96	
3[a,c]	10	20	1	89	
4[a,c]	10	110	2	90	
5[b,c]	5	60	31	96	
6[b,c]	10	60	25	91	
7[b,c]	15	60	43	97	
8[b,c]	20	60	33	97	
11[b,c]	25	60	40	98	
12[b,c]	30	60	26	90	
13[b,c]	40	60	23	88	
14[b,c]	80	60	8	87	
15[b,d]	15	60	38 ± 8	90 ± 10	
16[b,c]	15	60	2	95	
17[b,c]	15	60	13		91
18[b,c,e]	15	60	41	95	
19[b,c,e]	15	60	13		91

[a]Acidification prior addition of TBAF (entries 1–4, Route 1). [b] Route 2. [c]Average of two experiments. [d]Average of ten experiments. [e]Automated synthesis system. [f]Calculated as amount of radioactivity in Vial B compared to the total radioactivity delivered from the cyclotron. [g]RCY determined by radio-HPLC.

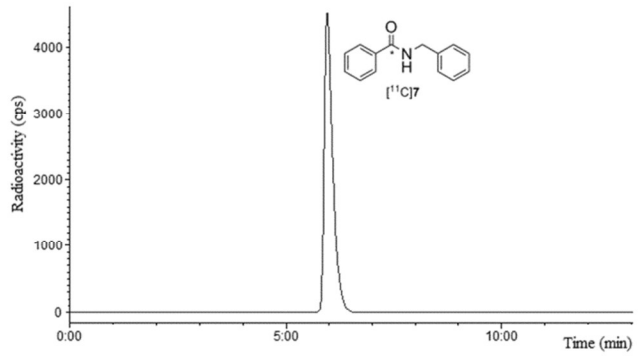


Fig. 1 HPLC radiochromatogram of crude [^{11}C]**7** in Vial B.

In order to demonstrate the utility of the developed methodology an automated procedure was implemented using an Eckert & Ziegler Modular-Lab system (**Fig. 3**, See SI for experimental details). Using this apparatus both [^{11}C]**7** (**entry 18**) and [^{11}C]**CX546** (**entry 19**) were obtained with >90% RCYs (6 min after EOB).

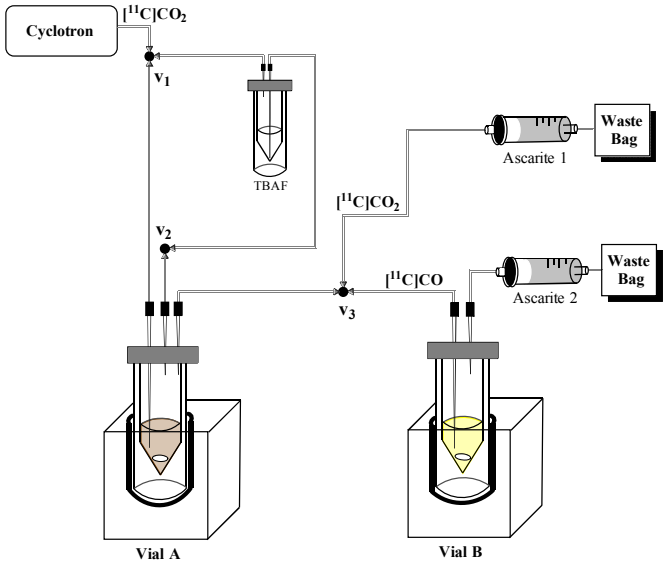


Fig. 3 Automated synthesis system for the two-vial setup.

Based on these findings, we propose that [^{11}C]CO_2 is trapped by silane lithium chloride species (**2b**) forming the [^{11}C]silane carboxylate ([^{11}C]**3b**). After TBAF addition, [^{11}C]**3b** rearranges to complex **I**, which in turn produces complex **II**. The subsequent [^{11}C]CO release from complex **II** is initiated by TBAF which triggers the intramolecular rearrangement producing salt **III** and [^{11}C]CO release. This is in agreement with the mechanism described by Brook *et al.* for the release of CO from silane derivatives.[10]

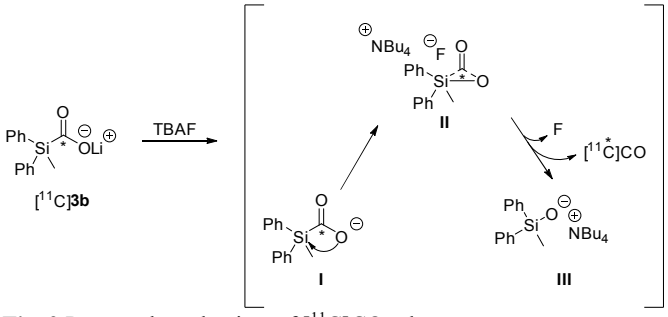


Fig. 2 Proposed mechanism of [^{11}C]CO release.

In conclusion, a rapid and reliable method for the chemical conversion of [^{11}C]CO_2 to [^{11}C]CO using a simple two-vial setup has been developed. This represents the first application of a [^{11}C]silane derivative as a [^{11}C]CO source for radiosynthetic applications. Cyclotron-produced [^{11}C]CO_2 was quantitatively trapped in Vial A (98%) at 20 °C. Upon TBAF addition, complete depletion of [^{11}C]**3b** was obtained (**Fig. SI1B**). The released [^{11}C]CO reacted rapidly and efficiently in Pd-mediated [^{11}C]carbonylation reactions. Crude [^{11}C]**7** and [^{11}C]**CX546** were obtained in high RCYs (≥97% and ≥90%, respectively) at 40 °C in short reaction times (6 min after EOB). Furthermore, the automated system was successfully developed and tested for the production of [^{11}C]**7** and [^{11}C]**CX546**.

Given the novelty and simplicity of this setup, the methodology has the potential to enable the widespread routine utilisation of [^{11}C]CO in different chemical reactions[2,14,15] leading to a wide range of PET tracers and their application for *in vivo* imaging.

Notes and references

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21 This work describes a method development study using short cyclotron irradiations where obtaining high specific activities (SA) were not the main focus. However, the associated carrier content of compound [^{11}C]**7** was in the range of 27–37 µmol. Assuming that the stable ^{12}C carrier content would be in the same range for a standard clinical [^{11}C]CO_2 production, it is estimated that specific activities of 70–90 GBq/µmol would be obtained. These are consistent with the SA's observed for other ^{11}C-labelled tracers at our institution.
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