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COMMUNICATION

[\textsuperscript{11}C]CO\textsubscript{2} to [\textsuperscript{11}C]CO Conversion Mediated by [\textsuperscript{11}C]Silanes: A Novel Route for [\textsuperscript{11}C]Carbonylation Reactions

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A novel chemical methodology is described for the conversion of [\textsuperscript{11}C]CO\textsubscript{2} to [\textsuperscript{11}C]CO. Diphenylmethyl silanes trap [\textsuperscript{11}C]CO\textsubscript{2} and release [\textsuperscript{11}C]CO rapidly when triggered by TBAF. Released [\textsuperscript{11}C]CO was used to produce [\textsuperscript{11}C]V-benzylbenzamide and AMPA receptor ligand, [\textsuperscript{11}C]CX546, in radiochemical yields >90\% within 6 min from [\textsuperscript{11}C]CO\textsubscript{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.\textsuperscript{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.\textsuperscript{1,3} Despite these requirements and the inherent toxicity of CO, it is still widely used for the synthesis of many functionalised molecules.\textsuperscript{1,3}

CO can be produced by the reduction of carbon dioxide (CO\textsubscript{2})\textsuperscript{4} using electrochemical,\textsuperscript{5} photochemical,\textsuperscript{6} thermal\textsuperscript{7} or chemical methods.\textsuperscript{8-11} The chemical conversion of CO\textsubscript{2} into CO relies on the ability of specific molecules to form a complex with CO\textsubscript{2}. These complexes release CO via an internal molecular rearrangement under specific reaction conditions. Examples include silanecarboxylic derivatives,\textsuperscript{10,11} heterocyclic carbenes,\textsuperscript{12} copper-boryl and copper-silyl\textsuperscript{13} complexes: so-called CO\textsubscript{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.\textsuperscript{10,11,13} By comparison, the other CO\textsubscript{2}–CO converting reagents have been shown to be more sluggish in releasing CO.\textsuperscript{8-10}

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

Initially, experiments were performed to identify a silane derivative able to trap [\textsuperscript{11}C]CO\textsubscript{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 [11C]CO$_2$ directly from the cyclotron in high efficiency (~98%) giving [11C]3b with a radiochemical yield (RCY) of up to 85% (Fig. SIIA).

A simple two-vial setup was used to trap [11C]CO$_2$ and convert it to [11C]CO (Vial A in Scheme 1 and Fig. S12) which was subsequently consumed in a Pd-mediated [11C]carbonylation reaction (Vial B in Scheme 1, example 1) producing [11C]N-benzylbenzamide ([11C]7).

The formation of [11C]CO release was obtained from [11C]7 in Vial B monitored by radio-HPLC (Fig. 1).

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 S11). Initial experiments used HCl to acidify [11C]3b prior to addition of TBAF (2 mmol, Route 1 in Scheme 1).

Only small amounts (2%) of [11C]CO was released from [11C]4b at 60 °C (Table 1, entry 1). The effect of different TBAF equivalents and temperatures were subsequently examined. Increased [11C]CO release was obtained from [11C]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 [11C]CO release (Table 1, entries 3 and 4).

The effect of [11C]3b protonation was subsequently investigated (Scheme 1). Surprisingly, the [11C]CO production (Route 2 in Scheme 1) increased from 4% to 25% when TBAF (10 mmol) was added at 60 °C without acidifying [11C]3b prior to fluoride source addition (Table 1, entries 2 and 6). Upon TBAF addition, the complete depletion of [11C]3b was observed (Fig. S11B).

This encouraging result suggested that the acidification of [11C]3b, prior to TBAF addition, inhibited [11C]CO release. Consequently, the effect of different TBAF concentrations (5–80 mmol) and the time course monitoring of [11C]CO release were examined. The highest [11C]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 [11C]CO release from Vial A was measured by monitoring the trapping of [11C]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 [11C]CO transfer to Vial B was achieved (Fig. S13, See SI for experimental details). This is consistent with the result obtained by radio-HPLC showing the complete depletion of [11C]3b after TBAF addition (Fig. S11B).

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

Radio-HPLC analysis of the reaction mixture in Vial B confirmed the production of [11C]7 with high RCYs of 98% (Table 1, Fig. 1 and Fig. S14).

In order to explore the applicability of the developed method in producing functionalised tracers, the synthesis of a selective AMPA receptor ligand, [11C]CX546, was successfully achieved (Scheme 1, example 2). [11C]CX546 was produced with RCYs >90% after 6 min from end of cyclotron [11C]CO$_2$ bombardment (EOB) (entry 17, Fig. S15).


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1 Acidification prior addition of TBAF (entries 1–4, Route 1). 2 Route 2. 3 Average of two experiments. 4 Average of ten experiments. 5 Calculated as amount of radioactivity in Vial B compared to the total radioactivity delivered from the cyclotron. 6 RCY determined by radio-HPLC.
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 $[^{11}C]CNX546$ (entry 19) were obtained with $>90\%$ RCYs (6 min after EOB).

Based on these findings, we propose that $[^{11}C]CO_2$ is trapped by silane lithium chloride species ($[^{2}b]$ forming the $[^{11}C]$silane carboxylate ($[^{11}C]3b$). After TBAF addition, $[^{11}C]3$ 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.$^{19}$

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. S11B). The released $[^{11}C]CO$ reacted rapidly and efficiently in Pd-mediated $[^{11}C]$carbonylation reactions. Crude $[^{11}C]7$ and $[^{11}C]CNX546$ 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 $[^{11}C]CNX546$.

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.$^{14,15}$ 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 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 $^{11}$CO2 production, it is estimated that specific activities of 70–90 GBq/µmol would be obtained. These are consistent with the SAs observed for other $^{11}$C-labelled tracers at our institution.
22 This work was supported by European Commission, FP7-PEOPLE-2012-ITN (316882, RADIOMI) and Medical Research Council (MRC, MR/K022733/1). The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King’s College Hospital NHS Foundation Trust. The authors would like to thank Dr. Robin Fortt for his technical assistance. Moreover, the authors would like to thank the referees for their suggestions to improve the manuscript.