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^{11}C-carbonylation reactions using gas–liquid segmented microfluidics†

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A novel gas–liquid segmented microfluidic platform has been developed. The Pd-mediated ^{11}C-carbonylation reaction proceeds smoothly on this platform and good to excellent radiochemical conversions (RCC) were observed. Twelve compounds were successfully radiolabelled using this novel technology, including the well established D_2 receptor radioligands [^{11}C]raclopride and [^{11}C]FLB 457.

[^{11}C]Carbon monoxide (^{11}CO), derived from the positron emitting nuclide ^{11}C ($t_{1/2} = 20.4$ min), is an attractive synthon in PET (Positron Emission Tomography) radiochemistry,[1] as the carbonyl group is present in most biologically-relevant molecules. Consequently, a great deal of research efforts has been devoted to developing efficient and simple methods for its introduction, *e.g.* high-pressure reactors,[2] xenon gas carrier,[3] ^{11}CO trapping solutions,[4] reactive catalytic species,[5] oxidant reagents[6] and backed-tube reactors.[7] In our long-term objective to improve general access to this synthon, we turned our attention to microfluidic (MF) technology with its well documented advantages over conventional batch reactions.[8] In particular, multi-phase MF, which offers advantages such as large interfacial areas, fast mixing, precision temperature control and reduced mass-transfer limitations. Two distinctly different flow conditions exist for gas–liquid MF reactions. The first condition is commonly referred to as annular flow and is characterized by a gas flow in the centre of a liquid film coated on the internal surface of the reactor. The second flow condition is called segmented flow and relies on the continuous formation of micro-bubbles within the liquid flow. In general, the segmented flow approach provides better control over reaction condition and more importantly have proven to reduce the formation of Pd particles, which clog the MF channel.[9]

MF is a rapidly growing field within PET radiochemistry,[10] however, until this day, its application in ^{11}C-radiochemistry remain rather unexplored. In 2004, Lu *et al.* reported the first ^{11}C-synthesis using a MF approach.[11] A glass fabricated, T-shaped micro reactor was used to study the liquid–liquid MF reaction of carboxylic acids with [^{11}C]methyl iodide as methylating agent. More recently, Miller *et al.* presented a Pd-mediated carbonylative protocol to ^{11}C-labelled products, using a gas–liquid MF approach.[12] The heterogeneous reaction was performed by generating an annular flow of ^{11}CO/N_2 inside a 5 m long serpentine-shaped micro channel, prefilled with coupling reagent solution. Later, a commercially available MF device was used to perform liquid–liquid phase ^{11}C-carbonylation reactions, in which a liquid solution of Cu(Tp*)^{11}CO was applied as CO donor.[13] The system was applied in the synthesis of the neuropeptide Y5 receptor antagonist, [^{11}C]MK-9233.[14]

In this communication we report the first application of a gas–liquid segmented MF protocol allowing direct access to an array of ^{11}C-labelled drug-like amides. In addition to the labeling of [^{11}C]amides, the protocol also demonstrated its utility in the radiosynthesis of a [^{11}C]carboxylic acid and three [^{11}C]esters.

The MF system (Fig. 1) used in this study consists of a precision syringe pump, a μ-mass flow controller, a mixing-tee to permit gas-to-liquid contact, and a 5 m fused-silica capillary

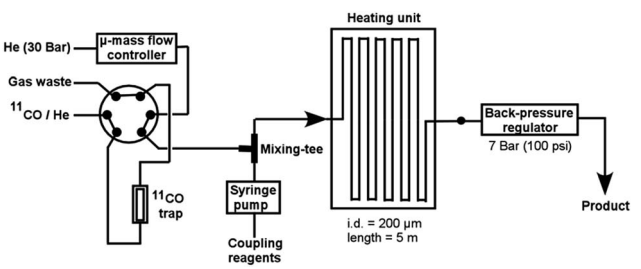

Fig. 1 Schematic diagram of the microfluidic system.

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reactor (inner diameter (i.d.) = 200 μm) located within a pre-heated oil bath, as well as a back-pressure regulator (100 psi, BPR). In a typical reaction, ^{11}CO was trapped and concentrated on a small silica column at −196 °C. The accumulated ^{11}CO was subsequently transferred into the MF reactor using the μ-mass flow controller charged with helium as carrier. At the same time a premixed solution of coupling reagents (aryl halide, Pd-ligand and amine in anhydrous THF) was infused into the MF reactor using the syringe pump. A leak-tight gas bag was connected to the outlet of the product vial to receive volatile radioactive products (*e.g.* ^{11}CO). The fully automated synthesis process was controlled and monitored using in-house developed software (for full experimental details see the ESI†).

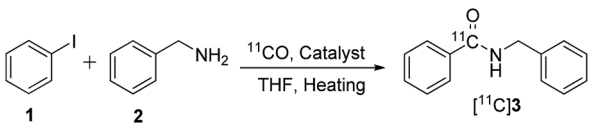
Initially, experiments were performed at different flow rates using a micro mixing-tee (i.d. = 50 μm) in order to identify conditions with sufficient gas-to-liquid interfacial area. Thus, a series of experiments was performed using the synthesis of *N*-benzyl-[carbonyl-^{11}C]benzamide ([^{11}C]**3**) as a model reaction using $Pd(PPh_3)_4$ as catalyst. As expected, the RCC of [^{11}C]**3** was strongly dependent on the gas-to-liquid flow rates. For example, by decreasing the gas flow from 200 μL min^{-1} to 100 μL min^{-1} while keeping the liquid flow constant (20 μL min^{-1}), a close to 3-fold improvement in RCC was observed (Table 1, entries 1 and 2). Next we examined the reaction at different temperatures. No notable improvement was observed at 120 °C (Table 1, entry 3) compared to 100 °C. Attempts to perform the reaction at lower temperatures resulted in decreased ^{11}CO trapping efficiency and thereby lower RCC (Table 1, entry 4). On the other hand, a quantitative conversion to the desired product was observed already at room temperature (r.t.) using Pd_2(cinnamyl)Cl_2–xantphos as catalyst (Table 1, entry 6). This further illustrates the utility of Pd_2(cinnamyl)Cl_2–xantphos in ^{11}C-aminocarbonylation reactions.[5] During the course of the condition screening, we experienced issues related to clogging of the micro mixing-tee. In order to improve the robustness of the method, we decided to test a mixing-tee with a larger inner diameter (i.d. = 150 μm). Further alterations to the conditions were thus conducted (Table 1, entries 7–9). To our delight, at 100 °C, a gas flow of 100 μL min^{-1}, liquid flow of 30 μL min^{-1} using $Pd(PPh_3)_4$ as catalyst, [^{11}C]**3** was obtained in a reproducible RCC of 95 ± 1% (Table 1, entry 8).

Furthermore, in order to explore the applicability of the developed method, the best conditions (Table 1, entries 5 and 8) were first applied in synthesis of a variety of ^{11}C-labelled test compounds (Scheme 1, compound [^{11}C]**3–7**). All reactions showed high ^{11}CO trapping efficiency (>95%) and the test compounds were produced in a RCC range of 79–99%.

Finally, a series of drug-like amides were successfully radiolabelled using the methodology (Scheme 1, compound [^{11}C]**8**–[^{11}C]**14**). In general, good RCCs were observed when using $Pd(PPh_3)_4$ as catalyst, as exemplified by the well established D_2 receptor radioligand, [^{11}C]FLB 457 [15] ([^{11}C]**8**), which was produced in a RCC of 61 ± 4% with a near quantitative ^{11}CO trapping efficiency. However, for [^{11}C]**13** and [^{11}C]raclopride[16] ([^{11}C]**14**) $Pd(PPh_3)_4$ was found ineffective as a catalyst. For these molecules, the more active Pd_2(cinnamyl)Cl_2–xantphos catalytic system provided RCCs of 41 ± 1% and 79 ± 1%, respectively. The present MF platform has now been operated conveniently over 100 times without any experiences with clogging. When comparing the synthesis of [^{11}C]**13** in the current work with the previously reported gas–liquid annular MF approach,[12] we observe a 12% increase in RCC with our setup. We attribute this finding to the larger gas–liquid interface generated using the gas–liquid segmented approach. An enlarged photo of the fused-silica capillary is shown in Fig. 2, in which this flow profile is confirmed.

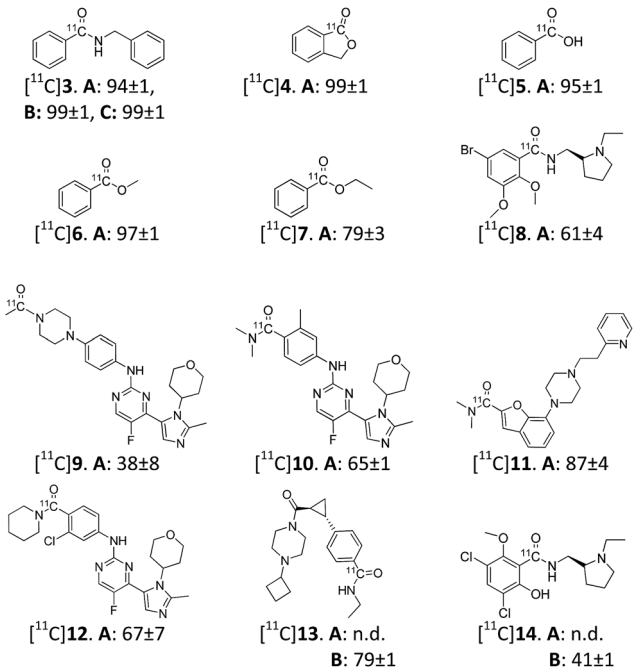
PET radioligands for *in vivo* human use are typically produced in gigabecquerel (GBq) quantities, therefore, as a final statement to the utility of this method, two compound ([^{11}C]**12**, **13**) were produced on a preparative scale. Production data are

Table 1 Condition screening using *N*-benzyl-[carbonyl-^{11}C]benzamide as a model reaction



Entry[a]	*T* (°C)	Gas flow (μL min^{-1})	Liquid flow (μL min^{-1})	Mixing tee (i.d., μm)	Catalyst	Trapped ^{11}CO[b] (%)	RCP[c] (%)	RCC[d] (%)
1	100	200	20	50	$Pd(PPh_3)_4$	53	71	37
2	100	100	20	50	$Pd(PPh_3)_4$	>99	96	95 ± 2[e]
3	80	100	20	50	$Pd(PPh_3)_4$	89	67	59
4	120	100	20	50	$Pd(PPh_3)_4$	>99	94	93
5	100	100	20	50	Pd_2(cinnamyl)Cl_2–xantphos	>99	99	99
6	r.t.	100	20	50	Pd_2(cinnamyl)Cl_2–xantphos	>99	98	98
7	100	100	20	150	$Pd(PPh_3)_4$	95	91	86
8	100	100	30	150	$Pd(PPh_3)_4$	>99	96	95 ± 1[e]
9	100	200	30	150	$Pd(PPh_3)_4$	91	90	82

[a] Reaction conditions: iodobenzene (20 μmol), benzylamine (50 μL), Pd-source (14 μmol), ligand (14 μmol), THF (1 mL), 100 °C. [b] Decay corrected; the fraction of radioactivity left in the crude product after purging with nitrogen. [c] Radiochemical purity determined by radioanalytical HPLC. [d] Radiochemical conversion based on the total radioactivity delivered to the collection vial. [e] Average of two runs.



Scheme 1 Compounds produced using the gas–liquid segment microfluidic approach. Conditions A: aryl-halide, nucleophile, $Pd(PPh_3)_4$, THF, 100 °C. Conditions B: aryl-halide, nucleophile, Pd_2-(cinnamyl)Cl_2, xantphos, THF, 100 °C. Conditions C: iodobenzene, benzylamine, [$PdCl_2$–(xantphos)], toluene, 100 °C. Average of two runs.

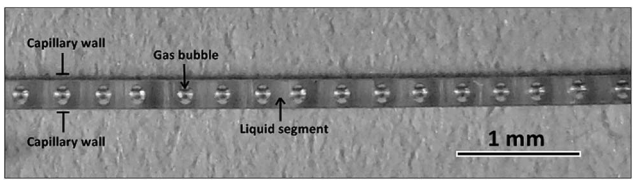
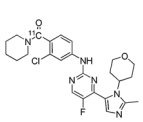
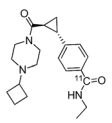


Fig. 2 Photographic image of the flow profile inside the fused-silica capillary.

summarized Table 2. All compounds were produced in sufficient radioactivity amounts (1200 and 2800 MBq), and with high radiochemical purity (RCP, >99%) and moderate specific radioactivity (SRA, 40 and 54 GBq μmol^{-1}).

Table 2 Isolated yields of compounds synthesized using the gas–liquid segmented ^{11}C-carbonylation reaction

Product	Isolated yield (MBq)	SRA (GBq μmol^{-1})	RCP (%)	Synthesis time (min)
	1200	40	>99	49
	2800	54	>99	52

Conclusions

In summary, a novel gas–liquid segmented microfluidic approach to the synthesis of ^{11}C-carbonyl labelled compounds has been developed. To our knowledge this represents the first application of gas–liquid segmented microfluidics within the field of PET radiochemistry. The suitability of this technique was demonstrated with the synthesis of twelve different ^{11}C-labelled compounds, including the well established D_2 receptor radioligands [^{11}C]raclopride and [^{11}C]FLB 457.

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