### 11C-Carbonylation Reactions Using Gas-Liquid Segmented Microfluidics

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11C-Carbonylation Reactions Using Gas-Liquid Segmented Microfluidics

Kenneth Dahl, Magnus Schou, Johan Ulin, Carl-Olof Sjöberg, Lars Farde and Christer Halldin

A novel gas-liquid segmented microfluidic platform has been developed. The Pd-mediated 11C-carbonylation reactions 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 D2 receptor radioligands [11C]raclopride and [11C]FLB 457.

[11C]Carbon monoxide (11CO), derived from the positron emitting nuclide 11C (t1/2 = 20.4 min), is an attractive synthon in PET (Positron Emission Tomography) radiochemistry, as the carbonyl group is present in most biologically-relevant molecules. Consequently, a great deal of research efforts has been devoted into developing efficient and simple methods for its introduction, e.g. high-pressure reactors, xenon gas carrier, 11CO trapping solutions, reactive catalytic species, oxidant reagents and backed-tube reactors. 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. 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.

MF is a rapidly growing field within PET radiochemistry, however, until this day, its application in 11C-radiochemistry remain rather unexplored. In 2004, Lu et al. reported the first 11C-synthesis using a MF approach. A glass fabricated, T-shaped micro reactor was used to study the liquid-liquid MF reaction of carbonylic acids with [11C]methyl iodide as methylating agent. More recently, Miller et al. presented a Pd-mediated carbonylative protocol to 11C-labelled products, using a gas-liquid MF approach. The heterogeneous reaction was performed by generating an annular flow of 11CO/N2 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 11C-carbonylation reactions, in which a liquid solution of Cu(Tp+)11CO was applied as CO donor. The system was applied in the synthesis of the neuropeptide Y5 receptor antagonist, [11C]MK-9233.

In this communication we report the first application of a gas-liquid segmented MF protocol allowing direct access to an array of 11C-labelled drug-like amides. In addition to the labeling of [11C]amides, the protocol also demonstrated its utility in the radiosynthesis of a [11C]carboxylic acid and three [11C]esters.
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 contact. Thus, a series of experiments was performed using the synthesis of N-benzyl-[carbonyl-\(^{11}\text{C}\)]benzamide \((\text{1.1.1})\) as a model reaction using Pd(PPh\(_3\))\(_3\) as catalyst. As expected, the RCC of \((\text{1.1.1})\) was strongly dependent on the gas-to-liquid flow rates. For example, by decreasing the gas flow from 200 µl/min to 100 µl/min while keeping the liquid flow constant (20 µl/min), 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}\text{C}\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 \(^{11}\text{C}\)-aminocarbonylation reactions.\(^7\) 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

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### Table 1 Condition screening using N-benzyl-[carbonyl-\(^{11}\text{C}\)]benzamide as a model reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Gas flow (µl/min)</th>
<th>Liquid flow (µl/min)</th>
<th>Mixing tee (i.d., µm)</th>
<th>Catalyst</th>
<th>Trapped (^{11}\text{CO}) (%)</th>
<th>RCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>200</td>
<td>20</td>
<td>50</td>
<td>Pd(PPh(_3))(_3)</td>
<td>53</td>
<td>71 / 37</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>100</td>
<td>20</td>
<td>50</td>
<td>Pd(PPh(_3))(_3)</td>
<td>&gt;99</td>
<td>96 / 95±2(^a)</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>100</td>
<td>20</td>
<td>50</td>
<td>Pd(PPh(_3))(_3)</td>
<td>89</td>
<td>67 / 59</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
<td>100</td>
<td>20</td>
<td>50</td>
<td>Pd(PPh(_3))(_3)</td>
<td>&gt;99</td>
<td>94 / 93</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>100</td>
<td>20</td>
<td>50</td>
<td>Pd(_2)(cinnamyl)Cl(_2)-xantphos</td>
<td>&gt;99</td>
<td>99 / 99</td>
</tr>
<tr>
<td>6</td>
<td>r.t.</td>
<td>100</td>
<td>20</td>
<td>50</td>
<td>Pd(_2)(cinnamyl)Cl(_2)-xantphos</td>
<td>&gt;99</td>
<td>98 / 98</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>100</td>
<td>20</td>
<td>150</td>
<td>Pd(PPh(_3))(_3)</td>
<td>95</td>
<td>91 / 86</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>150</td>
<td>Pd(PPh(_3))(_3)</td>
<td>&gt;99</td>
<td>96 / 95±1(^a)</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>200</td>
<td>30</td>
<td>150</td>
<td>Pd(PPh(_3))(_3)</td>
<td>91</td>
<td>90 / 82</td>
</tr>
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\(^a\) 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.

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### Scheme 1 Compounds produced using the gas-liquid segment microfluidic approach.

- **A**: aryl-halide, nucleophile, Pd(PPh\(_3\))\(_3\)-THF, 100°C.
- **B**: aryl-halide, nucleophile, Pd\(_2\)(cinnamyl)Cl\(_2\)-xantphos, THF, 100°C.
- **C**: iodobenzene, benzylamine, [PdCl\(_2\)-(xantphos)], Toluene, 100°C. Average of two runs.
thus conducted (Table 1, entries 7 - 9). To our delight, at 100°C, a
gas flow of 100 µl/min, liquid flow of 30 µl/min using Pd(PPh₃)₄ as
catalyst, [¹¹C]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 [¹¹C]-labelled test compounds
(Scheme 1, compound [¹¹C]3 - 7). All reactions showed high [¹¹C]
trapping efficiency (> 95 %) and the test compounds were produced
in a RCC range of 79 – 99%.

In summary, a novel gas-liquid segmented microfluidic
approach to the synthesis of [¹¹C]-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 [¹¹C]-labelled compounds, including the well
established D2 receptor radioligands [¹¹C]raclopride and
[¹¹C]FLB 457.

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 ([¹¹C]12-13) were
produced on a preparative scale. Production data are 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).

### Conclusions

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

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Johnström and Dr. Vladimir Stepanov. We also thank all
members of the PET group at Karolinska Institutet for all their
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### Notes and references

† Footnotes relating to the main text should appear here. These
might include comments relevant to but not central to the
matter under discussion, limited experimental and spectral data,
and crystallographic data.

§ Footnotes, etc.

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