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Citation

As Published
http://dx.doi.org/10.1021/ol1026848

Publisher
American Chemical Society (ACS)

Version
Author's final manuscript

Accessed
Sun Dec 16 20:01:13 EST 2018

Citable Link
http://hdl.handle.net/1721.1/76277

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Continuous Flow Coupling and Decarboxylation Reactions Promoted by Copper Tubing

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Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT

A convenient and efficient flow method for Ullmann condensations, Sonogashira couplings, and decarboxylation reactions using a commercially available copper tube flow reactor (CTFR) is described. The heated CTFR effects these transformations without added metals (e.g., Pd), ligands, or reagents, and in greater than 90% yield in most cases examined.

In recent years organic synthesis has been impacted greatly by the rapid growth of innovative technologies such as microwave-assisted heating, polymer-supported reagents/catalysts, and continuous flow processes. Among these developments, continuous flow chemical synthesis has emerged as an important alternative to traditional batch synthesis and enjoyed considerable use in both academic and industrial laboratories. Compared to batch, flow offers several distinct benefits including efficient mixing, precisely controlled reaction parameters, automated reaction processes, the ability to perform reactions at high temperatures and high pressures, and ease of scale-up. Many previously challenging or hazardous reactions can now be safely and efficiently conducted in flow. In addition, flow synthesis methods can be combined with other enabling technologies to improve efficiency and productivity significantly. As

part of our efforts to develop methods of chemical synthesis in flow, we now report a simple and expeditious means for conducting a variety of useful copper-promoted reactions using a commercially available copper tube reactor.  

![Figure 1](image1.png)

**Figure 1.** (A) A copper flow coil. (B) A high-temperature CTFR with the top metal jacket removed (1.0 mm i.d. tubing). (C) Heated CTFRs using a standard Vapourtec R4 heating module.

The copper tube flow reactor (CTFR) that we employed is made of a coil of copper tubing with 1.0 mm i.d. (inner diameter). (Figure 1A). The coil is wound around an open mesh support and, when inserted into a glass jacket, can be heated by circulated air to 150 ºC using a standard Vapourtec R4 heating module. The copper tubing can be heated safely up to 250 ºC when a glass jacket, can be heated by circulated air to 150 ºC using a standard Vapourtec R4 heating module. The copper tube flow reactor (CTFR) that we employed is made of a coil of copper tubing with 1.0 mm i.d. (inner diameter). (Figure 1A). The coil is wound around an open mesh support and, when inserted into a glass jacket, can be heated by circulated air to 150 ºC using a standard Vapourtec R4 heating module.

High temperature protiodecarboxylation reactions must be performed in a tube reactor heated to the same temperature (entry 3), suggesting that the copper tubing was promoting the reaction. Other parameters were then quickly tuned in flow, and the optimal conditions are shown in entry 2. The CTFR approach was more efficient than microwave and batch reactions with traditionally used catalysts (entries 4-6).

**Table 1.** Ullmann coupling of 1a and 2a

<table>
<thead>
<tr>
<th>entry</th>
<th>method</th>
<th>T (ºC)</th>
<th>residence time (min)</th>
<th>flow rate (mL/min)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>copper tube</td>
<td>150</td>
<td>30</td>
<td>0.33</td>
<td>69%</td>
</tr>
<tr>
<td>2</td>
<td>copper tube</td>
<td>150</td>
<td>20</td>
<td>0.17</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>PFA tube</td>
<td>150</td>
<td>30</td>
<td>0.33</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>microwave</td>
<td>150</td>
<td>30</td>
<td>-</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>microwave</td>
<td>150</td>
<td>30</td>
<td>-</td>
<td>31%</td>
</tr>
<tr>
<td>6</td>
<td>oil bath</td>
<td>90</td>
<td>90</td>
<td>-</td>
<td>40%</td>
</tr>
</tbody>
</table>

* Flow conditions: 1a (2.0 mmol, 1.0 M), 2a (2.4 mmol, 1.2 M). Conversion is based on 1H NMR analysis of crude materials.  

We then applied this protocol to couplings of several aryl halides and amines. In general, 250 psi backpressure regulator was used to ensure that acetonitrile could be safely heated well above its boiling point without flashing. The trace amounts of copper leached from the tubing were efficiently removed with Quadrupreme™ Thionine (QD-TU). As illustrated in Table 2, both alkyl amines and N-containing heterocycles were effective coupling partners. Reactions using less methods that do not use added ligands, such as that described below, can generally be more attractive.  


(12) See Supporting Information for trace copper analyses.

(13) QP-TU was purchased from Aldrich (product number 655422).
reactive aryl bromides proceeded smoothly (entries 1 and 5). These conditions were also effective for the Ullmann-Goldberg amide synthesis (entries 6 and 7).

Table 2. Synthesis of arylamines in CTFR

| Entry | Ar= | R¹ | R² | Conversion | Yield%
|-------|-----|----|----|------------|-------|
| 1     | Ph= | x1 | i-Pr | 100% | 74%
| 2     | Ph= | x1 | Cl | 100% | 76%
| 3     | 3a  | 3b | 80% | 76%
| 4     | 3c  | 3d | 100% | 76%
| 5     | 3c  | 3e | 55% | 76%
| 6     | 3c  | 3f | 98% | 96%
| 7     | 3c  | 3g | 98% | 86%

* Reaction conditions: A solution of I (1.0 M), 2 (1.20 M) and TBAA (1.10 M) in CH3CN was injected from pump at 0.17 mL/min, two 10 mL CFTR were connected using a standard PFA tubing (1.0 mm i.d.), 0.1 mL/min flow rate, 200 min residence time; Conversion is based on $^1$H NMR analysis of crude materials; Isolated yields after flash chromatography on silica gel.

Encouraged by the preliminary results, we next turned our attention to the Sonogashira cross-coupling reaction, particularly methods in which Pd was not used. After some experimentation in heated CFTR, we learned that solvent choice was a key parameter in flow. DMF was found to be appropriate, but other solvents such as CH3CN, THF, EtOAc, and EtOH resulted in precipitation and subsequent system blockage during the reaction. We found that TBAA, the organic base also used for the Ullmann-type reactions (vide supra), was again more effective than other commonly used bases (e.g., Et3N, Hünig’s base, Et3NH, n-BuNH2; see Supporting Information for details). A general protocol was thus developed, and a range of arylalkynes were constructed in good yields (Table 3). When trimethylsilyl acetylene was employed as the nucleophile, the reaction required a catalytic amount of palladium (entry 5). Notably Hay-Glaser coupling byproducts (symmetrical 1,3-dienes) were not observed in any case, possibly attributable to the flow reaction format (rate of alkyne addition and short residence time).

Table 3. Synthesis of arylalkynes in CFTR

| Entry | Ar= | R= | Conversion | Yield%
|-------|-----|----|------------|-------|
| 1     | Ph= | 4a | 90% | 90%
| 2     | Ph= | 4b | 98% | 90%
| 3     | Ph= | 4c | 100% | 92%
| 4     | Ph= | 4d | 90% | 85%
| 5     | Ph= | 4e | 100% | 94%
| 6     | Ph= | 4f | 87% | 76%

* Reaction conditions: A solution of I (1.0 M), 4 (1.20 M) in DMF and a stock solution of TBAA (1.10 M) in DMF was mixed through pumps into a T-mixer at a total flow rate of 0.33 mL/min; 0.50 mol % Pd(PPh3)4Cl2 was added; reaction was heated at 120 ºC. Conversion is based on $^1$H NMR analysis of crude materials; Isolated yields after flash chromatography on silica gel.

We also examined the use of high-temperature CFTR for protiodecarboxylation reactions. Traditional batch processes involve the use of copper powder or copper (I) salts at elevated temperatures and, in some cases, even above 250 ºC. Moreover, the release of CO2 gas generated in the reaction at such temperatures, raises significant safety concerns, particularly when carrying out large scale syntheses in batch. We speculated that flow reactors would provide us with a more controlled process because only a small amount of gas would be generated and liberated from the system at any given time. As illustrated in Table 4, decarboxylation reactions

of many aromatic and heteroaromatic substrates were successfully achieved at 250 °C in CTFR without any additional catalysts, ligands or additives. In the case of 5-fluorindole-2-carboxylic acid, 2.0 equiv of quinoline and longer reaction time were required (entry 6).

Table 4. High-temperature protiodecarboxylation reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>t (min)</th>
<th>Yield</th>
<th>Ar</th>
<th>t (min)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>15</td>
<td>90%</td>
<td>5</td>
<td>50</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>30</td>
<td>94%</td>
<td>6</td>
<td>240</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>30</td>
<td>98%</td>
<td>7</td>
<td>50</td>
<td>92%</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>30</td>
<td>98%</td>
<td>8</td>
<td>50</td>
<td>92%</td>
</tr>
</tbody>
</table>

* Reaction conditions: A solution of 6 (1.0 M in NMP) was injected from pump; † Residence time; ‡ Isolated yields with purity > 95% (1H NMR spectroscopy); ‡ 2.0 equiv of quinoline was added, experiment was set up in recycling mode at 1.0 mL/min flow rate.

In summary, we have demonstrated the effectiveness of commercially available CTFR for several important copper-mediated transformations including Ullmann condensations (no added supporting ligand), Sonogashira couplings (no added Pd) and protiodecarboxylation reactions by way of a simple and more environmentally benign procedure. The reactor itself acts as a source of fresh copper metal and can be safely heated at high temperatures and high pressures. When experiments performed under same conditions in PFA or stainless steel tube reactors, reactions failed to give any desired products, suggesting a promoting effect of the copper tubing. In many cases, the crude reaction products can be used further in multistep processes without additional purification.

Acknowledgment. The authors thank the NIBR Education Office for a Presidential Postdoctoral Fellowship to Y. Z. and Global Discovery Chemistry (GDC) for financial support. The authors are grateful to Dr. Laetitia Martin (NIBR-Basel) and Dr. Damien Webb (Massachusetts Institute of Technology) for helpful discussions. The authors thank Ms. Penny Wright (NIBR-Horsham) for trace copper analyses and the analytical group at GDC-Cambridge for NMR spectroscopy and HRMS assistance. The authors are indebted to Duncan Guthrie, Chris Butters and Adam Whyatt (Vapourtec Ltd.) for useful suggestions and support.

Supporting Information Available Complete experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.