FlowSyn™ Application Note 3:
Knorr Pyrazole Synthesis

\[
\begin{align*}
\text{CF}_3\text{O} & \quad \text{HCl} - \text{DMF} \\
\text{CF}_3\text{O} & \quad \Delta \\
\text{NHNH}_2 & \quad \text{3 (Mw = 288)}
\end{align*}
\]

**Method:**

**System solvent:** 10% Aqueous DMF.

**Stock solution A:** 0.20M 4,4,4-Trifluoro-1-phenyl butane-1,3-dione **1** (4.32g, 20.0 mmol) in DMF (100 mL) or 0.40M **1** (4.32g 20.0 mmol) in DMF (50 mL).

**Stock solution B:** 0.20M Phenylhydrazine (2.38g, 22.0 mmol) containing 1M HCl (25.0 mL, 25 mmol) in DMF (75 mL) or 0.44M **2** (4.76g, 44.0 mmol) containing 2M HCl (25.0 mL, 50 mmol) in DMF (75.0 mL).

A 0-300 psi variable back-pressure regulator was fitted and used in all experiments.

**a. Flow Optimisation using ‘Manual Control’ Interface**

1. FlowSyn™ was fitted with a 2.5 mL PTFE tubing reactor, and the heating unit was tensioned to ensure optimal thermal contact.

2. The inlets were both set to ‘Solvent’, the outlet was set to ‘Waste’, and the system was calibrated by running each pump at 1.00 mL/min for 5 min and collecting the outflow in a measuring cylinder. The measured volumes were entered into the ‘Configuration’ screen.

3. A series of flow experiments were performed under ‘Manual Control’ to profile the condensation reaction (Figure 1). These experiments examined the dependence on temperature and stoichiometry, and also the effect of residence time ($R_t$).

4. In each case, the flow reactor was allowed to equilibrate to the set temperature with the selection valves set to ‘Solvent’. The valves were then set to ‘Reagent’ and the system was allowed to reach steady state for 1.5 reactor volumes before a sample (2 drops) was collected and diluted with MeCN (1.0 mL) in a mass spec. vial. The samples were analysed by HPLC and UVLC-MS (AUC relative) to identify the components of the product mixture.

5. Finally, the selection valves were again set to ‘Solvent’, the temperature was set to 20°C, and the system was flushed through and allowed to cool down to ambient temperature with the cooling gas on for approximately 0.5 h.

The optimisation data obtained is shown in Figure 1 and illustrates that, as would be expected, pyrazole formation is temperature dependent. In particular, the reaction proceeds most efficiently at 100°C (note: this is higher than the recommended maximum temperature for PTFE tubing reactors of 80°C, and consequently the backpressure was set to a low value to compensate and limit distortion of the reactor). Under these conditions, the reaction is complete and all the 1,3-diketone starting material **1** is consumed within a 10 min residence time. However, an excess of phenylhydrazine **2** is necessary to achieve this.

In an attempt to improve throughput further, it was determined that the residence time could be halved ($R_t = 5$ min) if the concentrations of the starting materials were doubled. This did not introduce any adverse insolubility issues, presumably attributable to the use of DMF as solvent.
The conditions shown in red (column 7) were selected for scale-up and correspond to a throughput of 38 mmol/h.

b. Flow Scale-up using 'Start Experiment' Interface

FlowSyn™ is equipped with a program that allows unattended operation and is able to run a flow experiment automatically, stopping the instrument when the reaction is complete. This was used to perform an 8 fold scale-up flow hydrolysis of 1 under the optimised conditions above.

1. FlowSyn™ was fitted with a 20 mL PTFE tubing reactor cassette, and the heating unit was tensioned to ensure optimal thermal contact.
2. The 'Collect' outflow from the collection valve was directed into a collection bottle.
3. The selection valves were set to 'Reagent' and the reagent lines were primed.
4. The selection valves were set to 'Solvent' and the system was primed to remove all air bubbles. The pumps were calibrated at 1.00 mL/min as previously [no further adjustments were necessary].
5. The following flow parameters were entered into the 'Setup Experiment' screen.

<table>
<thead>
<tr>
<th>Reactors:</th>
<th>Coil</th>
<th>Reaction Time:</th>
<th>5.00 min (00:05:00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coil Type:</td>
<td>User</td>
<td>Total Flow Rate:</td>
<td>4.00 mL/min</td>
</tr>
<tr>
<td>Coil Temp:</td>
<td>100°C</td>
<td>Volume A:</td>
<td>40 mL</td>
</tr>
<tr>
<td>Col. Temp.</td>
<td>0°C</td>
<td>Volume B:</td>
<td>60 mL</td>
</tr>
<tr>
<td>Pressure:</td>
<td>30 psi</td>
<td>A:B Ratio:</td>
<td>1.0:1.5</td>
</tr>
<tr>
<td>Inlet A:</td>
<td>R</td>
<td>Post Collect:</td>
<td>22.0 mL</td>
</tr>
<tr>
<td>Inlet B:</td>
<td>R</td>
<td>Post Wash:</td>
<td>22.0 mL</td>
</tr>
</tbody>
</table>

Reaction time = 25 min

6. Pressing 'Run Experiment'. FlowSyn™ equilibrates to the set temperature and then runs the flow experiment, before finally cleaning the system by flushing with system solvent ('Post Wash').
7. The collected outflow was neutralised by adding solid sodium hydrogen carbonate, then filtered and the solvent evaporated in vacuo. The residual oil was treated with water (100 mL) and 10% HCl to precipitate a solid which was washed on a filter with further HCl (2 x10 mL) and then water (2 x 20 mL) before air drying. Finally, the red solid obtained was washed with cold hexanes (1 x 10 mL) and dried o/n @ 50°C in vacuo to leave 3 as a beige powder (3.85g, 84%): m.p. = 94-96°C.

Throughput = 38.0 mmol/h (10.9g/h).

UVLC-MS (ESI +ve): (m/z 289.12 (MH+)); Rₚ = 3.62 min, >99%

IR (ATR): 1594(w), 1495(m), 1473(m), 1445(m), 1377(m), 1234(m), 1119(s), 1098(s), 977(m), 750(s), 692(s) cm⁻¹;

¹H NMR (CDCl₃, 400 MHz): δH 7.2-7.35 (m, 8H), 7.12-7.16 (m, 2H), 6.68 (s, 1H).
Supplementary Information:

Figure 2. Schematic FlowSyn™ configuration used.