A Non-Resonant Microwave Applicator for Continuous Flow Chemistry: Safe, Fast Optimization and Scale-Out Synthesis

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Introduction

We hereby present proof of principle organic reactions utilizing a combination of \textbf{continuous flow} chemistry and \textbf{controlled microwave heating} allowing organic synthesis in small scale and subsequent scale-out without scale-up translation (Figure 1). The system utilizes a novel \textbf{non-resonant} microwave heating applicator purpose-built for continuous flow that heats an entire reactor \textbf{without pronounced hot and cold spots} along the reactor (Figure 2, left).

Figure 1. Schematic view of the ArtheniusOne™ prototype.

Results

The equipment was evaluated by optimization and scale-out of different types of relevant chemical organic reactions using a 3 mm ID reactor (Scheme 1-5), followed by scale-out using a 6 mm ID reactor (Scheme 6-7).

Scheme 1. Pd(II)-catalyzed styrene synthesis (results by Odell et al.\textsuperscript{1} in parenthesis).

\begin{align*}
\text{Scheme 2. Pd(0)-catalyzed Suzuki-Miyaura coupling.}
\end{align*}

\begin{align*}
\text{Scheme 3. Oxathiinozole synthesis of bioactive M. tuberculosis protease inhibitor.}
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\begin{align*}
\text{Scheme 4. Fischer indole synthesis (results by Razzaq et al.\textsuperscript{2} in parenthesis).}
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\begin{align*}
\text{Scheme 5. Claisen rearrangement (results by Razzaq et al.\textsuperscript{2} in parenthesis).}
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\begin{align*}
\text{Scheme 6. Fischer indole synthesis (results by Razzaq et al.\textsuperscript{2} in parenthesis).}
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\begin{align*}
\text{Scheme 7. Claisen rearrangement (results by Razzaq et al.\textsuperscript{2} in parenthesis).}
\end{align*}

Equipment

The equipment consists of a microwave generator and a microwave applicator that transfers the generated energy to the reaction mixture. A consumable tubular borosilicate reactor, available in 1 to 6 mm ID dimensions, is housed inside the applicator through which the reaction mixture passes. The generator output of 0-150 W is linked with five IR sensors positioned along the reactor while the microwave frequency is automatically adjusted at 2.4-2.5 GHz to adapt to the loss tangent value of the reaction mixture, ensuring rapid software-controlled heating (Figure 2, right). The components of the equipment are depicted in Figure 3.

Figure 2. Left: Infrared image of a 3 mm ID reactor heating the Pd(II)-catalyzed styrene synthesis reaction mixture from Scheme 1 at a temperature of 200 °C. Right: Temperature profile during the heating of NMP to 190 °C.

Figure 3. Left: Consumable tubular borosilicate reactor (3 mm ID). Right: The ArtheniusOne™Flow system prototype, consisting of microwave generator and microwave applicator from WaveCraft AB, together with Binary Pump Module (BPM) from Uniqsis Ltd.

Conclusions

We have presented proof of principle applications for a novel non-resonant continuous flow microwave system. The fast heating, small reactor volume and rapid change of reaction temperatures “on-the-fly” are unique features of this instrumentation. We believe the non-resonant system to be an unprecedented laboratory tool for safe and fast optimization work and scale-out synthesis.