PRECISE CONTROL OF THE REIMER-TIEMANN REACTION USING INTEGRATED HEATING AND THERMOCHROMIC LIQUID CRYSTALS

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Abstract
Microreactors incorporating thin film resistive heating elements for continuous flow organic synthesis are presented. Internal thermal conditions were monitored in real time using reflectance spectra of temperature sensitive thermochromic liquid crystals (TLC) in a collateral microfluidic network. To demonstrate the precise temperature control provided by this method, the thermal optimisation of the Riemer-Tiemann formylation of β-naphthol was performed under hydrodynamic pumping regimes.

Keywords: heating, liquid crystals, microreactor, organic synthesis

1. Introduction
The Reimer-Tiemann reaction,[1] utilized in the formylation of activated aromatic rings, suffers from two major drawbacks, firstly, the biphasic nature of the system acts to limit the reaction interface. Inefficient transfer of reagents between these layers may stifle the rate of reaction and decrease yields. Secondly, to obtain a satisfactory reaction rate, the process should be performed at reflux. However, if reflux occurs within an enclosed microfluidic structure the contact time in the mixing device becomes drastically reduced. As the solvents boil they expand rapidly, leading to the premature expulsion of the reaction mixture from the chip. The generation of gases also prevents down stream on-line analysis. To maximise the reaction efficiency without boiling, the temperature within the microreactor channels must be carefully maintained and monitored.

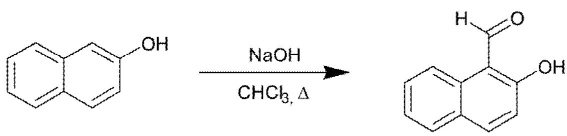

Figure 1.The Riemer-Tiemann formylation.

In heated syntheses, it is important to determine whether the measured temperature corresponds to the actual temperature in the reaction channel due to the exponential relationship between temperature and reaction rate. In the case of an exothermic reaction, the reaction may progress more aggressively than predicted, which may lead to the

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production of undesirable byproducts. Measurement of chip temperature has been performed previously by integration of platinum temperature sensitive resistors.[2] However, in microfluidic channels where heat transfer coefficients are high, the temperature difference between the channel and the bulk material may differ considerably. Additionally, this may be accentuated by the difference in the thermal conductivities of the chip material and the fluid filled portion of the device. Ideally, a method for in-channel temperature determination should reflect the temperature condition within a microfluidic channel directly. The method should be rapid to implement and flexible, requiring minimal additional support equipment.

Thermochromic liquid crystals are molecules that demonstrate properties of both liquids and solids and exhibit a number of phases between these two extremes. The transition between phases is triggered by heat and results in a colour change due to the chiral nature of the molecule. Standard products are available covering a range of start temperatures from -30°C to +120°C and a colour bandwidth from 0.5°C to 40°C allowing either a broad or precise temperature indication over a wide temperature range for the rapid accumulation of experimental data in heat transfer studies and thermal mapping.

3. Experimental

Nickel-gold thin film resistive heating elements on a glass substrate were fabricated by evaporative deposition. To ensure an even temperature distribution and efficient transfer of heat to the microfluidic channels, each turn of the meandering fluidic channel was mirrored by the heating element in such a way that each part of the fluidic network was equidistant from the heating element. The integration of TLCs into a microfluidic reactor for in channel temperature measurement was achieved by the introduction of an additional collateral microfluidic channel. With similar dimensions and thermal properties as the reaction channel, the temperature experienced by the TLC occupying the second channel should be comparable to that of the reaction channel assuming the characteristic dimension for heat transfer is maintained. The TLCs were introduced to the channel as a polymer bead slurry facilitating handling and offering similar thermal conductivity properties to that of the fluid filled reaction channel. The colour spectrum exhibited by the TLC's spans the visible spectrum between 400 and 750 nm. To allow for precise temperature monitoring, the reflectance spectra of

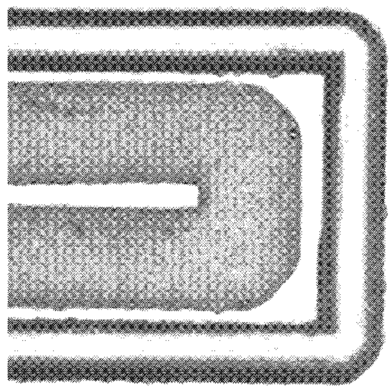

Figure 2. TLC beads occupying a collateral microfluidic channel

the TLCs were acquired using a high sensitivity fibre optic spectrometer (AVS-S2000, Avantes Inc.) To obtain a spectrum, a halogen lamp fitted with a light guide (Leica GLS100) was used to illuminate the device. A 100 μm OD fibre optic was positioned perpendicular to the TLC using a micrometer controlled translation stage and reflectance spectra were recorded with a resolution of ≈0.5 nm. Calibration data for temperature verses the wavelength of peak reflectance were obtained by recording spectra from a chip containing TLC immersed in an oil bath and heated over a range of temperatures.

For the continuous-flow formylation of phenols solutions of β-naphthol (1.25g, 8.7 mmol) in ethanol (3 mL) and chloroform (1.6g, 13.4 mmol) and 25% sodium hydroxide (2.5g, 62.5 mmol) in water (5ml) were prepared. These solutions were introduced into two inlets of the heated reactor chip at a flow rate of 5.0 $\mu Lmin^{-1}$ using a syringe pump (Harvard Apparatus). The reaction was quenched immediately upon exiting the chip outlet in 12% hydrochloric acid. Product analysis was performed by GC-MS without further purification by comparison to spiked standardised solutions.

4. Results and discussion

From the reflectance spectra of the TLC between 60 and 70°C an exponential relationship between peak reflectance wavelength and temperature was observed. Although this temperature range is not large, it was adequate to indicate the critical temperature such that reaction reflux was avoided. Over the temperature range of interest (60 to 65°C), temperature may be determined to within 0.2°C. Beyond this point, temperature resolution decreases as the rate of wavelength change with temperature decreases. However, each spectrum is composed of a number of overlapping peaks. These peaks could be analysed using a muliti-wavelength algorithm as opposed to a single peak maximum, leading to improved temperature resolution across a broader temperature range.

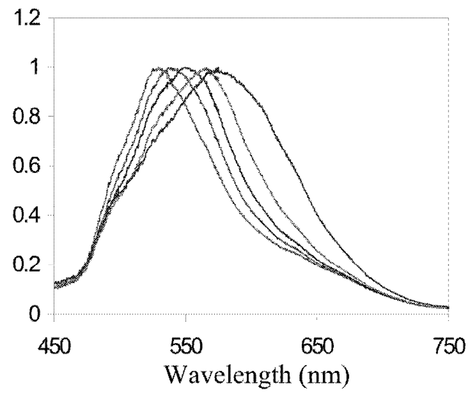

Figure 3. Variation in TLC reflectance spectra between 60 and 65°C

To study the effect of temperature on the Reimer-Tiemann reaction in a continuous flow microfluidic device, the formylation of β-naphthol was performed at set flow rates over a range of temperatures (Figure 1). Conventionally in a macroscale open vessel, an exponential relationship between rate and temperature is expected. As predicted, upon increasing the reaction temperature in a microreactor a corresponding increase in reaction

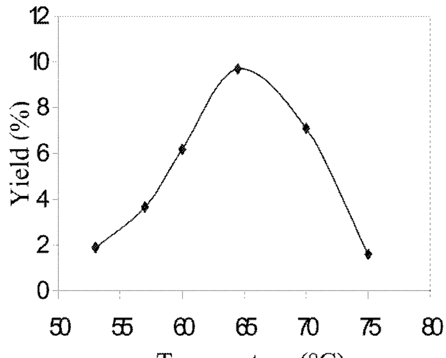

Figure 4. The effect of excess heat in an enclosed channel on reaction yield

rate was observed. However, as the boiling point of the solution was approached, thermal expansion and boiling led to severely decreased residence times. This is illustrated in figure 4, which demonstrates the observed yield variation with increasing temperature in the microreactor. The use of TLCs in microreactor devices allows such reactions to be performed at optimal thermal conditions for increased reaction yields on-chip. Although the yields observed in these initial experiments were lower than those usually obtained on the macroscale, neither flow rate nor reagent concentration were optimised in this study.

5. Conclusions

The utility of thermochromic liquid crystals for accurate in-channel temperature determination and control in microfluidic devices has been demonstrated. TLCs are ideal for microfluidic applications as they enable temperature measurement of small microenivironments such as a fluidic channel to be monitored, the size of which is only limited in this example by the bead size and optical detection coupling. The potential of TLCs to be encapsulated in chemically inert polymers such as PTFE may also allow inclusion of the TLC directly into the reaction mixture and therefore temperature determination *in situ*. Although feedback control for these experiments was performed manually, the use of a miniaturised spectrometer allows for the facile integration of a computer regulated feedback loop for automated temperature control.[3]

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