

# ON CHIP GENERATION AND REACTION OF UNSTABLE INTERMEDIATES: MONOLITHIC MICROREACTORS FOR DIAZONIUM CHEMISTRIES

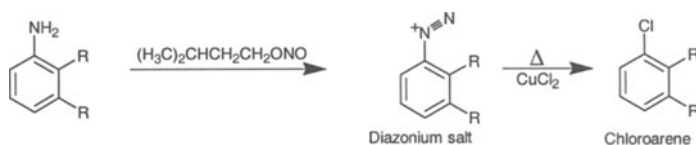
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## Abstract

Monolithic microreactors for the safe and expedient continuous synthesis of products involving unstable intermediates were fabricated and tested. The optimisation of diazonium salt formation in anhydrous conditions and its subsequent *in situ* chlorination using the Sandmeyer reaction (Scheme 1) in a microfluidic network under hydrodynamic pumping regimes is presented. Significant enhancement of yields was observed due to enhanced heat and mass transfer in microfluidic systems. Direct detection by Raman spectroscopy is demonstrated as a tool for on-line dynamic optimisation.

**Keywords:** organic synthesis, microreactor, continuous flow, hazard reduction



Scheme 1. Chloro-de-diazonation – the Sandmeyer reaction.

## 1. Introduction

The diazotisation of aromatic amines is an industrial process of great importance [1]; the range of functionalities that can be introduced via de-diazonation reactions being vast. The dangers of diazotisation are well known [2], diazonium salts being sensitive to physical agents such as heat, light, shock, static electricity, etc that can lead to rapid uncontrollable decompositions and explosions. Traditionally diazonium salts are prepared in aqueous conditions due to the stabilising effect of water on the diazonium salt and used without isolation limiting the applicability of the reaction to some substrates.

Dry diazonium chemistry can be performed on a monolithic micro-fluidic device (Figure 1) in complete safety as at any given instant the total volume of dry diazonium salt is measured in nanolitres. Using micro-

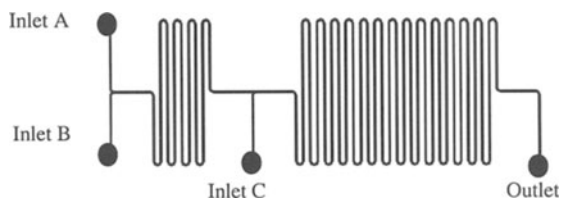


Figure 1. Schematic of microreactor channel. Channel depth 50  $\mu\text{m}$ , width 150  $\mu\text{m}$ , length 36 cm.

fluidic devices in continuous flow regimes, real-time on-line optimisation is possible using direct detection methods. This is demonstrated by the use of Raman spectroscopy for on-chip detection and optimisation of flow rates.

## 2. Results and Discussion

Monolithic microreactor structures combine two or more steps into a single device. Incorporating reagent mixing, quench addition and heated decomposition sections into one device decreases experimental complexity, minimises dead volumes and the problem of precipitation is overcome. In devices incorporating heated sections a steep thermal gradient is established due to the large surface to volume area of the device. This results in two entirely different temperature environments with a separation of only 20mm without the need for the inclusion of heat exchangers. For a typical structure flow rates of  $3.2\mu\text{Lmin}^{-1}$  through the first two inlets were used to allow for complete diffusive mixing and reaction over the first serpentine delay section.

By operating in continuous flow microreactors on-line and real-time optimisation of reaction conditions can be achieved by utilization of direct monitoring techniques. Raman spectroscopy utilises monochromatic light usually in the visible region of the spectrum and is an excellent real-time, on-line fingerprinting tool for chemical identification. Each channel can be addressed individually for facile reaction monitoring with little or no glass Raman signal background from the chip itself. To demonstrate the use of Raman spectroscopy for direct detection and dynamic optimisation of reaction conditions, solutions of aniline and isoamyl nitrite in N,N-dimethylformamide were infused into the device at a variety of flow rates (Figure 2). Both aniline and N,N-dimethylformamide have strong characteristic Raman bands between  $200$  and  $1700\text{ cm}^{-1}$  providing ample information for sample identification.[3] Raman spectra can be obtained at millimolar concentrations or below and at data rates of up to five spectra per second allowing on-line real-time reaction monitoring (Figure 3). Utilizing optimized concentration conditions chloro-de-diazonation was performed

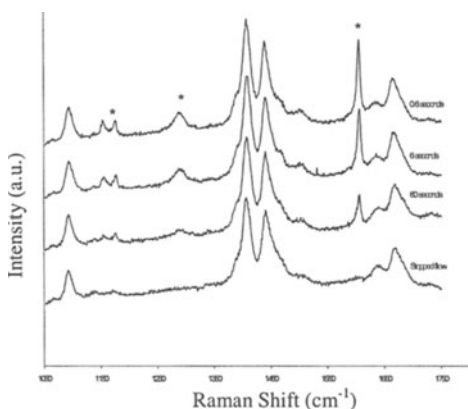


Figure 2. On-line reaction monitoring of aniline diazotisation by Raman spectroscopy

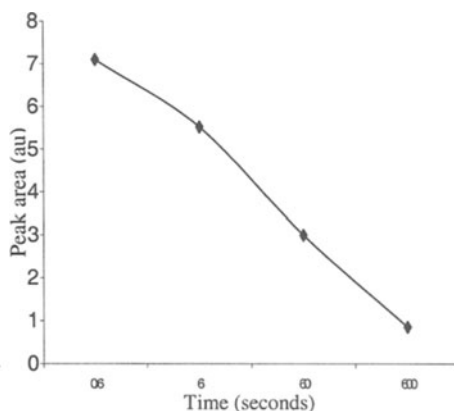


Figure 3. Dynamic optimization of aniline diazotisation by Raman spectroscopy

for three separate aryl amines on a microreactor each being diazotised by amyl nitrite following identical procedures. No attempt to optimize temperature conditions was made during this study nor was an acid catalyst employed. To affect diazotisation, isoamyl nitrite was chosen which is often used on a laboratory scale to perform diazotisations on water sensitive substrates.[4] Alkyl nitrites are thermally unstable and may readily decompose or explode on heating.[5] By using micro-reactor components, however, reagents such as alkyl nitrites can be utilised for industrial processes in relative safety. In addition utilizing alkyl nitrites often results in yields inferior to those utilizing sodium nitrite. Substrates containing alkyl groups such as the toluidines used in these experiments can also lead to disappointing yields. By operating in the micro-environment, microfluidic reactors may be used to increase yields of such reactions to more satisfactory levels. The advantages of microflow reactors can be clearly seen by comparison to a traditional bulk scale synthesis employing the same solutions and temperatures. In contrast to poorly mixed bulk solutions with little temperature control, yields of reactions performed on the microreactor showed significant improvement with increases of 15 - 20% being observed (Figure 4).

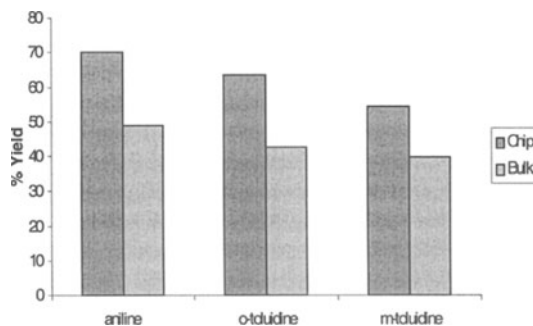


Figure 4. Comparison of nanoreactor vs bulk scale chloro-de-diazotisation.

### 3. Conclusion

The utility of a microfabricated microreactor to effect the safe, continuous flow multistage syntheses involving unstable, reactive intermediates has been demonstrated. The benefits of the technique include elevated temperature handling of thermally unstable intermediates and reagents in anhydrous conditions with increased safety over existing procedures. The simple structures described and the safe nature of the procedure show clear advantages over bulk scale syntheses with significant yield increases and facile optimisation offering a viable alternative to industrial routes.

### 4. References

1. The Chemistry of Diazonium and Diazo Groups; S. Patai Ed. Wiley, N.Y., (1978),
2. H. Zollinger, Diazo Chemistry I; VCH:Weinheim, pp. 24 (1994),
3. G. N. R Tripathi, J. Chem. Phys, 73, 11, pp. 5521-5530 (1980),
4. M. P. Doyle, B. Siegfried, J. F. Dellaria Jr., *Journal of Organic Chemistry*, 42, pp.2426-2431 (1977),
5. *SORB: safety relevant characteristic data of chemical materials*, pp.146. (1976).