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Continuous-Flow Generation of Anhydrous Diazonium Species: Monolithic Microfluidic Reactors for the Chemistry of Unstable Intermediates

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Abstract:

Monolithic microfluidic reactors for the safe, expedient, and continuous synthesis of products involving unstable intermediates were fabricated and assessed. The formation of diazonium salts in anhydrous conditions and their subsequent in situ chlorination within microfluidic channels under hydrodynamic pumping regimes is presented. Significant enhancements in yield were observed due to enhanced heat and mass transfer in microfluidic systems. Analysis performed using off-line GC and GC−MS was compared with on-line, on-chip Raman spectroscopy for the direct determination of analytes.

Introduction

The development of synthetic chemistry utilising microfluidic devices or microfluidic reactors has been of increasing interest in recent years. The term microfluidic reactor herein describes reactors with characteristic dimensions most conveniently measured in micrometers with instantaneous reaction volumes measured in the nanoliter to microliter range. Miniaturisation of reaction systems offers several advantages over the macroscale. These include improved mixing efficiencies and increased thermal transfer, leading to improved reaction selectivities, low sample consumption, and higher sample throughput per unit volume.[1]

In most conventionally scaled reactor vessels, mixing is achieved by turbulence or eddy flow. Fluid elements of varying sizes induced by inertial forces create a mixture that is highly segregated with a finely dispersed structure but still heterogeneous at the molecular level. The amalgamation of these fluid elements is then achieved by molecular diffusion over short intra-element distances. In typical microfluidic systems viscous forces outweigh inertial forces, and flow operates in the laminar flow regime. The transition between turbulent and laminar flow is conveniently characterised by the Reynolds number (equation 1), a dimensionless ratio of the inertial and viscous forces.

$$\mathrm{Re} = \frac{\rho(4(A/P))\nu}{\mu} \qquad (1)$$

Here ρ is the fluid density (kg m^{-1}), ν is the average linear velocity (m s^{-1}), A is the cross sectional area of channel (m^2), P is the wetted perimeter (m), and μ is the absolute fluid viscosity (kg m^{-1} s^{-1}). When Reynolds numbers are greater than 2000, turbulence is dominant, whereas at Reynolds numbers below 100, laminar flow is the norm. Between these extremes lies a transitional region showing both behaviours. In exceptional laminar flow systems the degree of mixing can vary with Reynolds number, even at values below 100. This is only the case where the reactor channel is designed to invoke nondiffusive mixing, as demonstrated recently by Liu et al.[2] who employed the use of chaotic advection for mixing at low Reynolds numbers. In most microfluidic systems the channel design provides a stable laminar flow environment, and consequently, mixing of reagents is achieved by random molecular diffusion alone. Knowledge of diffusion rates provides accurate information on the degree of mixing and therefore allows a high degree of control over the quantities and location of reagents.[3] This control can be understood by a comparison of reaction rates and diffusion rates. In reactions with rates that are fast compared to the rate of mixing, the reaction rate is independent of the rate constant (k) and is entirely dependent on the rate of mixing. The volume available for reaction is reduced from the volume of the entire reaction vessel to a plane between reacting streams. In this situation, designated the *diffusion regime*, the potential for the formation of secondary products is the greatest. In comparison, the mixing time in the *chemical regime* is fast compared to the reaction rate, and therefore mixing is complete before significant amounts of products are present. The entire reaction vessel is available for reaction, and the smallest amounts of secondary products are formed. By employing techniques such as multilamination,[4] microfluidic reactors can perform complete mixing in milliseconds, opening the way for extremely efficient high-throughput synthesis.

The scale-up of processes from the laboratory to bulk and fine chemical industries is often a complex and expensive operation where precautions must be taken to guard against

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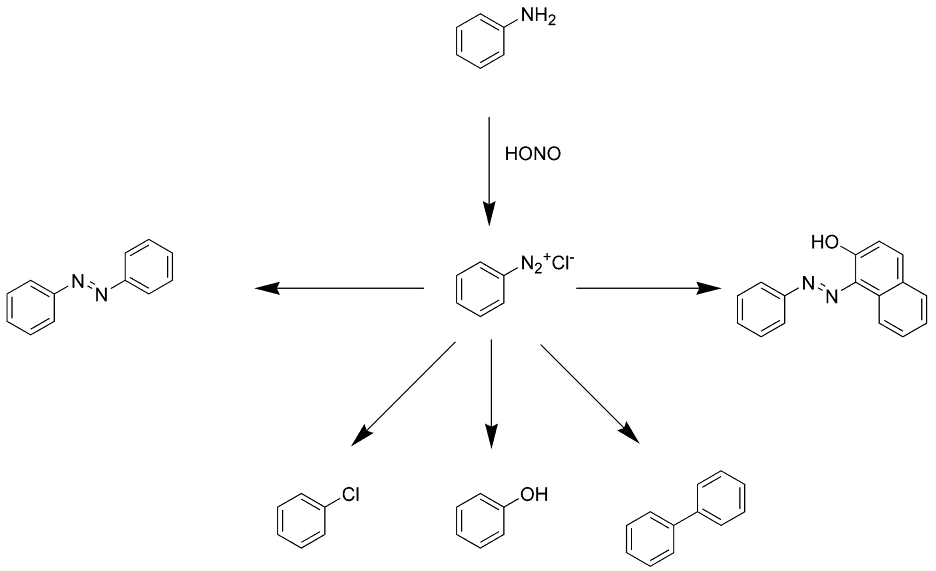
Scheme 1. **Synthetic transformations from a diazonium function**



reactive hazards and loss of reaction specificity. This is especially true when the process involves the use of reactive intermediates and events such as thermal runaway can lead to catastrophic consequences. By operating within microfluidic, continuous-flow regimes, precise manipulation of reagent concentration, temperature, and reaction times are possible, allowing greater control over the reaction. This reaction control is achievable due to the large surface area-to-volume ratios encountered on the microscale, allowing ultrafast heating and cooling of reactants. Manipulation of hazardous (e.g. toxic, pyrophoric, explosive, or unstable) compounds on the microscale also allows chemical reactions to be undertaken with increased safety due to the small instantaneous reaction volumes involved. These advantages have previously been demonstrated in the application of microfluidic reactor technology to the safe generation of singlet oxygen for the continuous-flow synthesis of ascaridole from α-terpinene.[5] Studies employing a microfluidic reactor showed that transformations of 85% or more were achievable with irradiation times of 5 s and the use of a low intensity light source. Furthermore, oxygenation and irradiation took place on-chip, leading to greatly enhanced safety.

Clearly dangerous reactions can be undertaken within microfluidic reactors in relative safety due to the small reacting volumes involved. These reactors can also be operated to produce large amounts of material if required. This is achieved using the concept of “scale-out”; where multiple microfluidic reactors are run in parallel to simulate a large-scale flow reactor without the usual problems associated with scaling. Scale-out can be seen as an answer to such problems as decreased yields on scale-up, low rate of maximum heat extraction, and the expense of high-pressure reaction vessels. The issues of microfluidic reactor scale-out have recently been addressed by researchers at MIT and DuPont who have begun construction of multiple reactor test stations for gas-phase systems.[6] These microfluidic reactor test stations contain not only microfabricated reactors but also other micro-engineered mechanical systems (MEMS) components for microfluidic control. A typical system may contain all the components of a conventional catalyst test station (feed gas manifold, reactor feed manifold, reactors, and control circuitry) but with a dramatically smaller footprint and a greatly reduced capital expenditure when compared with conventional reactor plants. This may not only decrease development time and costs but also create enough production flexibility for on-demand, on-site production, removing the need for storage of large quantities of dangerous chemicals. The application of microfluidic reactors to industrial processes has previously been shown by Krummradt et al. who examined an established multistage process for the generation of a fine chemical from the exothermic reaction between a carbonyl compound and an organometallic reagent.[7] In their study a microfluidic reactor pilot scheme was compared to a 0.5 L flask and a technical-scale vessel of 6000 L. The batch process was successfully transferred to a continuous flow, miniaturised reactor process, and increased yields were obtained. The production plant consisting of five parallel miniaturised reactors has been used in place of the conventional approach since August 1998.[7]

Motivated by these advantages, we describe herein the application of microfluidic reactor technology to the safe, efficient, continuous-flow chemistry of unstable intermediates. As a demonstration reaction for this study we chose the generation of diazonium reactive intermediates in anhydrous conditions and their subsequent on-chip reactive quenching. The diazotisation of aromatic amines is an industrial process of vast importance,[8] being useful for the synthesis of a wide range of species including azo compounds, biphenyls, hydroxyarenes, and chloroarenes (Scheme 1). The dangers of diazotisation are well-known: diazonium salts being sensitive to physical agents such as heat, light,

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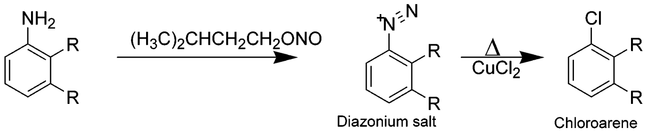
Scheme 2. **Chloro-dediazotisation, the Sandmeyer reaction**



shock, static electricity, and dehydration that can lead to rapid, uncontrollable decompositions and explosions.[9] Conventionally diazonium chemistry is performed on the bulk scale in quenching aqueous conditions. Diazonium chemistry can be performed on the bulk scale in anhydrous conditions but only by using diazonium tetrafluoroborates, certain arenediazonium sulfonates or in the presence of complex anions, e.g. zinc double chlorides and hexafluorophosphates.[10] Incidents of explosive decomposition of diazonium salts caused by salt deposition or vapour-phase reaction have been reported, and use of diazonium intermediates in industry is normally subject to stringent safety procedures.[11,12]

For processes that occur in two or more distinct steps, such as in the Sandmeyer reaction, the high degree of reaction control and increased safety mentioned above makes microfluidic reactors attractive for reaction optimisation and operation in a continuous-flow format. The difficulties involved in large-scale Sandmeyer syntheses are numerous (Scheme 2). These include the thermal instability of the diazonium intermediate, the evolution of large volumes of gas and the difficulties raised by interaction between mixed and unmixed strata in large vessels that can lead to unwanted coupling reactions. Furthermore, the aqueous conditions usually employed in diazonium synthesis limit the applicability of the reaction to some substrates. On a large-scale precise temperature control of process operations is needed. At temperatures above 283 K hydroxy-dediazonation is promoted to form the phenol in aqueous media.[13] In the case of reactive diazonium salts higher temperatures can lead to reaction of the parent arene in an explosive manner even under aqueous conditions.[14] However, at low temperatures the Sandmeyer reaction is often slow, leading to an increased likelihood of intermediate decomposition and cross-coupling reactions.

By using a microfluidic reactor the initial mixing of the nitrite and an amine can be carried out in complete safety. In addition, operating under continuous flow allows increased reaction control, which may lead to facile process optimisation, increased yields, and higher throughput per unit volume. For example, single-function reactor chips have previously been used to react preformed diazonium salts.[15] In addition, Harrison et al. described a system utilising preformed diazonium tetrafluoroborates for the formation of azo dyes under electrooosmotic flow (EOF) control.[16] Furthermore, a fast-flowing microfluidic reactor utilizing mixer vanes and heat exchangers for temperature control has also been patented by Clariant where azo dyes are produced in suspension by combination of a diazonium salt and coupling agent.[17]

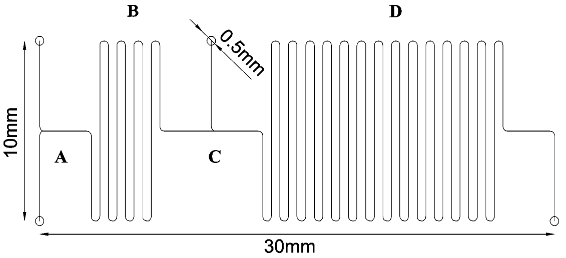


Figure 1. **Schematic of microfluidic reactor chip channel pattern used in all syntheses. Identities of components A−E provided in the text.**

Results and Discussion

In the current contribution, we demonstrate that hazardous, reactive diazonium salts, can be generated on-chip and used in situ in a safe and simple protocol. Initial experiments were undertaken using two separate microfluidic devices. First, the reagents for diazotisation were combined in a microfluidic mixer. The resulting fluid was then transported via a fused silica capillary interconnect to a heated microfluidic reactor for chloro-dediazonation. Although this approach exhibits the traditional advantages of modularity, the increased transport distances led to precipitation and furring of the capillary. A simpler and more elegant approach to performing sequential reaction operations is to minimise transport distances by incorporating both generation of the unstable intermediate and reactive quenching into a monolithic chip design, as previously demonstrated.[18]

By incorporating reagent mixing, quench addition, and heated decomposition operations onto a single device, transport distances and dead volumes are minimised preventing precipitation. This is realised in the current device (Figure 1) in the following way. The chip consists of a "tee" shaped inlet (A), a serpentine primary reaction sector 80 mm in length (B), a second inlet channel (C), a 280-mm long serpentine reaction sector at elevated temperature (D), and an exhaust (E) at which samples may be collected for analysis. The etched channels have an average depth of 50 μm and an average width of 150 μm and a total volume of 2.55 μL. In the current system incorporating localised heaters, a given fluid element can experience temperature variations in excess of 100 K s^{-1}. By virtue of the size of the channels used, the convective heat-transfer coefficient is extremely high (6×10^4 W m^{-2} K^{-1}). Although glass is not normally considered an efficient thermal conductor (thermal conductivity = 0.937 W m^{-1} K^{-1}), the overall heat-transfer

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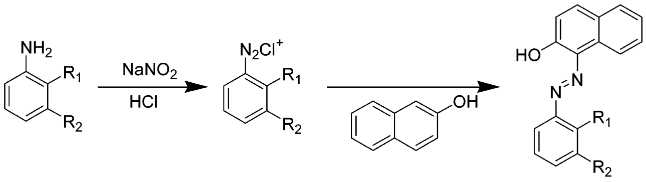
Scheme 3. **Formation of azo dyes via diazonium salts**



coefficient of the device remains competitive (740 W m^{-2} K^{-1}) when compared to bulk scale reaction vessels. Microfluidic reactors are also routinely fabricated from thermally conductive materials such as silicon, silver, and nickel. The combination of small channels and these thermally conductive materials provides extremely efficient heat dissipation (41 000 W m^{-2} K^{-1} for a silicon microfluidic reactor) and thus allows highly exothermic reactions to occur without risk of thermal runaway.

In a previous study we investigated the formation of diazonium salts by their in situ transformation into the azo dye Sudan 1 and its analogues (Scheme 3). Conversions ranging between 9 and 52% were calculated from the parent amine by extinction coefficient, where the extent of conversion is dependent on residence time and the substrate diazotised. These initial reactions were not optimised for the diazotisation reaction.[18] GC−MS data showed a close concordance between the extent of diazotisation of the aminoarenes and the conversion given above. This was ascertained from the presence of unreacted amine and insignificant amounts of byproducts from cross-coupling reactions, suggesting that optimisation of the diazotisation step would lead to enhanced reaction yields. This is additionally noteworthy as in continuous flow processing, nitrogen evolution during the chloro-dediazonation step has a considerable effect on the overall residence time of the reaction but has little effect on the more significant rate-determining diazotisation step.

The ability of the current microfluidic reactor to make available a range of previously restricted syntheses to the industrial chemist is confirmed by performing both the hydro and chloro-dediazonations in anhydrous conditions. Commonplace hydroxy-dediazonation is eliminated, and application to a far wider range of substrates becomes possible. The optimisation of the diazotisation step was studied by forming diazonium salts in anhydrous conditions with varying concentrations of isoamyl nitrite (1−15 mM) and amine (2−10 mM), followed by thermal hydro-dediazonation to the aryl substrate (Figure 2 and Table 1). To effect diazotisation, isoamyl nitrite was chosen which is often used on a laboratory scale to perform diazotisations on water-sensitive substrates.[19] Alkyl nitrites are thermally unstable and may readily decompose or explode on heating;[20] lower alkyl nitrites have even been known to decompose and burst the container in refrigerated storage. This has limited their use in large-scale synthesis. By using microfluidic reactor components, however, such materials can be utilised for industrial processes in relative safety.

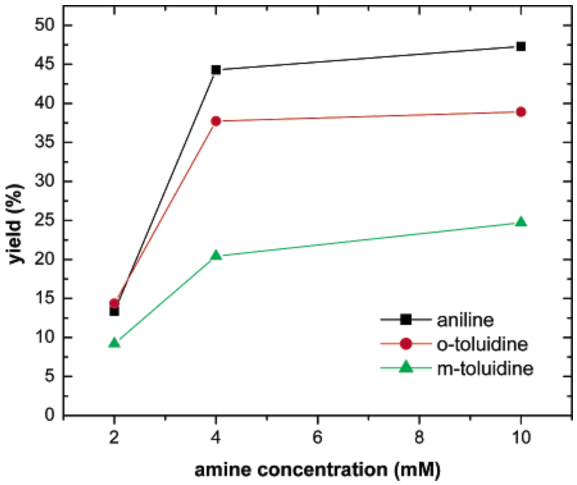


Figure 2. **Effect of amine concentration on product yield for the aromatic diazotisation/hydro-dediazonation reactions of aniline, *o*-toluidine, and *m*-toluidine. Isoamyl nitrite concentration = 10 mM.**

Table 1. **Effect of amyl nitrite concentration on product yield for aromatic diaszotisation/hydrodiazonation reactions**

substrate[a]	amyl nitrite (mM)	yield (%)
aniline	1.0	21.7
aniline	2.0	24.0
aniline	4.0	30.0
aniline	10.0	50.5
o-toluidine	1.0	7.7
o-toluidine	2.0	12.6
o-toluidine	4.0	20.8
o-toluidine	10.0	44.8
m-toluidine	1.0	6.7
m-toluidine	2.0	9.5
m-toluidine	4.0	14.5
m-toluidine	10.0	33.2

[a] Substrate concentration = 10 mM.

Inspection of Figure 2 and Table 1 shows that the extent of diazotisation is heavily dependent on both substrate concentration and isoamyl nitrite concentration. Higher concentrations of isoamyl nitrite were not studied due to the prohibitive viscosities of the reaction mixtures. Crude material from the microchip effluent was submitted to GC−MS analysis and demonstrated benzene and toluene as the majority products. Utilising optimised concentration conditions as determined for the diazotisation and hydro-dediazonation above, chloro-dediazonation was subsequently performed for three separate arylamines, each being diazotised by isoamyl nitrite under identical conditions. The ensuing reduction of the diazonium ion to the aryl radical and its halogen abstraction from cupric chloride was observed to be extremely efficient, resulting in conversion efficiencies of nearly 100%, as evidenced by GC−MS analysis of the chip effluent. This indicates that the extent of diazotisation of the aminoarenes and the conversion rates are closely related. Since the aim of this report is to demonstrate the utility and versatility of microfluidic reactors for synthetic optimisation, a full process optimisation of the Sandmeyer reaction was not performed. Furthermore, no attempt to optimise temperature conditions was made during this study,

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nor was an acid catalyst employed. It should be noted that Sandmeyer syntheses employing alkyl nitrites can result in yields inferior to those utilising sodium nitrite. In addition, substrates containing alkyl groups such as the toluidines used in these experiments often result in disappointing yields.[19]

Although attractive as a detection method, GC is an indirect and off-line approach to product analysis, results are typically obtained after transfer from the reaction vessel with analysis times typically in excess of 30 min. Direct monitoring techniques such as UV−vis absorption and FT-IR could be employed for monitoring the extent of diazotisation. However, as glass is the favoured medium for developmental organic chemistry these methods are impractical due to high extinction coefficients of glass in the UV and IR regions of the electromagnetic spectrum.

Raman spectroscopy utilises monochromatic light usually in the visible region of the spectrum and is an established real-time, on-line fingerprinting tool for chemical identification.[21] The combination of glass microfluidic reactors and Raman spectroscopy allows for the direct on-line detection of analytes in situ, without need of reaction quenching. Indeed, Raman spectroscopy has previously been used in microfluidic systems as a detection technique for electrophoretic separations in both capillaries and microfabricated channels.[22,23] It should be noted that, due to the curved nature of conventional capillary walls, scattered photons are increasingly dispersed, generally leading to a weakened Raman signal. However, the flat, uniform nature of microchannels and substrate surfaces in chip-based systems reduces scatter dispersion and ensures that scattered photons are collected only from the solution and not from the glass substrate.[23]

To demonstrate the use of Raman spectroscopy for the direct detection and dynamic optimisation of reaction conditions in microfluidic structures, solutions of aniline and isoamyl nitrite in *N*,*N*-dimethylformamide were infused into the microfluidic reactor at a variety of flow rates (Figure 2). Both aniline and *N*,*N*-dimethylformamide have strong characteristic Raman bands between 200 and 1700 cm^{-1}, providing ample information for sample identification (Table 2).[24] By monitoring for the extent of diazotization by the disappearance of aniline bands as opposed to the formation of the product, the reaction can be monitored in the forward mixing section, B. The problem of disruption of the Raman signal by evolved nitrogen bubbles is thus avoided.

For the reaction between aniline and amyl nitrite, inspection of the spectral region between 1050 and 1750 cm^{-1} illustrates direct evidence for the disappearance of aniline as a function of time. This is possible because, as stated above, the chloro-dediazonation reaction is near quantitative with respect to the parent diazonium salt. Thus, any direct monitor of the conversion of aniline serves as a marker for the extent of chloro-dediazonation. In particular, analysis of the in-plane ring-stretch band at 1603 cm^{-1} can be used to directly assess the extent of chloro-dediazonation as a function of reaction time (inset Figure 2). Interestingly, the disappearance of the in-plane ring-stretch band is shown to be complete after a residence time of 600 s. This is significantly longer than the residence time required for complete mixing on a microfluidic reactor as defined by the Fourier number for the system (0.55 for a flow rate of 3.1 $\mu\text{L min}^{-1}$ through each inlet at A). This indicates that the reaction is occurring in the chemical domain, rather than the diffusive domain. The utility of Raman spectroscopy for direct detection is further demonstrated by the speed of optimisation. The work required to establish the optimum residence time for the chloro-dediazonation on-chip using Raman spectroscopy involves a single reaction being monitored over 600 s. Spectral acquisition times are minimal, and data can be fed back to the pump very rapidly for the next run. In comparison, residence time optimisation by GC requires a series of reactions using significantly more reagents, each monitored in series over a range of reaction times taking up to 3 h to complete.

Table 2. **Vibrational exciton spectrum of aniline in DMF**[a]

Raman shift (cm^{-1})	molecular origin
1662	solvent (DMF)
1630	solvent (DMF)
1622	aniline (NH_2 bend a^1)
1603	aniline (ring stretch a^1)
1501	aniline (ring stretch a^1)
1468	aniline (ring stretch a^{11})
1443	solvent (DMF)
1408	solvent (DMF)
1279	aniline (x-sens a^1)
1176	aniline (CH bend ip a^{11})
1155	aniline (CH bend ip a^{11})
1095	solvent (DMF)

[a] Key: a^1 = In plane of symmetry, a^{11} = normal to plane of symmetry, x = NH_2, sens = sensitive, ip = in plane.

In terms of safety, the range of synthetic methods available, and the facility of optimisation, the advantages of microfluidic reactors can be clearly seen by comparison to a traditional laboratory-scale synthesis. In addition to these advantages, an increase in yield by utilisation of microfluidic reactors is also possible due to the high heat- and mass-transfer coefficients already mentioned. To compare and contrast reaction efficiency in a microfluidic reactor with a traditional laboratory method, a small-scale reaction flask of appropriate dimensions was employed, utilising the same solutions and reaction conditions.[19] In each case significant enhancement in yields on a microfluidic reactor (15−20%) were obtained in contrast to bulk solutions (Figures 3 and 4). Despite the relatively low flow rate used for the reaction, a space−time yield of 75 000 mol $\text{m}^{-3}\ \text{h}^{-1}$ is obtained due to the extremely small volume of the reactor.

Microfluidic Reactor Fabrication. The glass microchip (footprint 40 mm × 20 mm) was made in-house using direct-write laser lithography, wet chemical etching and bonding techniques as previously described.[25] Briefly, soda lime glass substrate precoated with a positive photoresist (AZ 1518)

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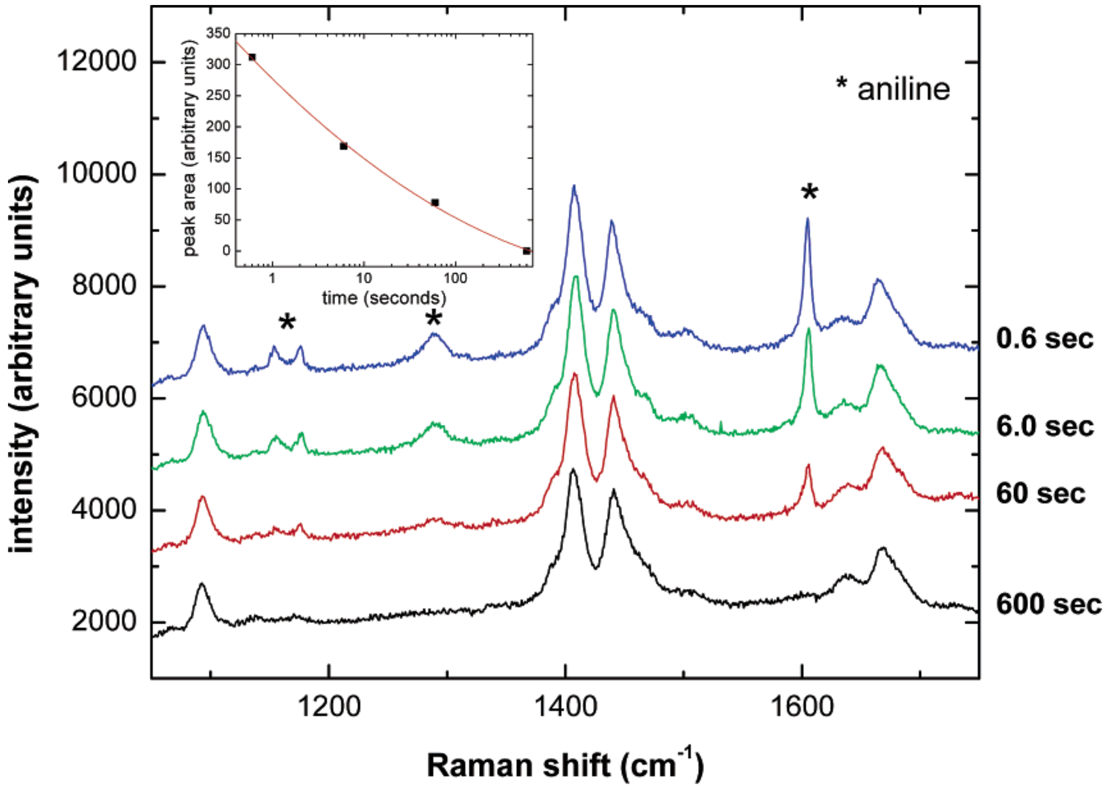

Figure 3. **Raman spectra of in-channel diazotisation reaction mixtures at various times after initial mixing. Inset shows the variation of the integrated area of the 1603 cm^{-1} peak as a function of reaction time.**

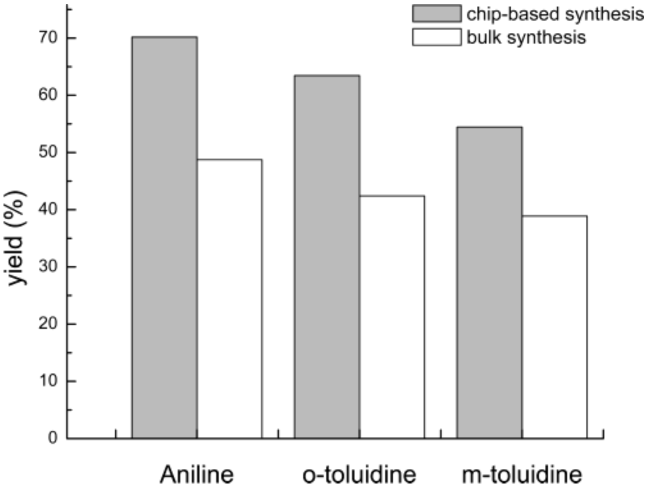

Figure 4. **Comparative product yields for the aromatic diazotisation/hydro-dediazonation reactions of aniline, *o*-toluidine, and *m*-toluidine using the microfluidic reactor and conventional bulk syntheses.**

and a low reflective chromium layer (Microfilm, Westlake Village, California) was exposed using a DWL system (DWL2.0, Heidelberg Instruments, Heidelberg, Germany) to transfer the channel design. After the photoresist was developed (Microposit 351, Shipley Europe Ltd, Coventry, UK), the channels were etched into the glass substrate using a buffered oxide etching solution (HF/NH_4F), and external access holes were drilled. To form enclosed channels, a glass cover plate cleaned with concentrated H_2SO_4 was thermally bonded in a furnace (Heraeus Instruments GmbH, Hanau, Germany) at 858 K. The reactor channel pattern is schematically described in Figure 1. Reynolds numbers for the microfluidic devices presented herein range between 1 and 2.1. This and the channel design ensure that only diffusive processes mediate mixing. To allow for complete diffusion over the serpentine sections, flow rates of 3.2 μL min^{-1} through the first two inlets were used with a balancing flow of 6.4 μL min^{-1} through the third inlet.

Experimental Section

Reagents and solvents were obtained from commercial sources and dried using 3 Å molecular sieves.

General Method for the Continuous-Flow Synthesis of Chloroarenes. Solutions of amine (0.1 mL, 1.1 mmol) in *N*,*N*-dimethylformamide (2 mL) and 97% isoamyl nitrite (0.35 mL, 2.6 mmol) in *N*,*N*-dimethylformamide (2 mL) were prepared. These solutions were introduced into inlets A of the reactor chip at a flow rate of 3.2 μL min^{-1} using a PHD 2000 syringe pump (Harvard Apparatus, Kent, U.K.). A solution of anhydrous copper (II) chloride (0.17 g, 1.3 mmol) in *N*,*N*-dimethylformamide (4 mL) was introduced into inlet B of the reactor chip at a flow rate of 6.4 μL min^{-1}, and the secondary serpentine section of the device was heated to 338 K. Heating of the secondary section was achieved by contacting the microfluidic reactor to a heated metal block. A continually moving stream of air cooled the first section of the device over both upper and lower surfaces. Product analysis was performed by GC without further purification by comparison to spiked standardised solutions giving a conversion by area analysis of 55−71%. GC−MS spectra were also obtained and showed concordance.

2-Chlorotoluene was prepared and analysed as above from *o*-toluidine (0.1 g, 1.1 mmol) in *N*,*N*-dimethylformamide (0.5 mL), isoamyl nitrite (0.35 mL, 2.6 mmol), and anhydrous copper (II) chloride (0.17 g, 1.3 mmol) in *N*,*N*-dimethylformamide (2 mL).

3-Chlorotoluene was prepared and analysed as above from *m*-toluidine (0.1 g, 1.1 mmol) in *N*,*N*-dimethylformamide (0.5 mL), isoamyl nitrite (0.35 mL, 2.6 mmol), and anhydrous copper (II) chloride (0.17 g, 1.3 mmol) in *N*,*N*-dimethylformamide (2 mL).

General Method for the Laboratory Synthesis of Chloroarenes.[19] To a solution of isoamyl nitrite (3.5 mL, 26 mmol) and anhydrous DMF (5 mL) heated at 338 K was added the aromatic amine (1 g, 11 mmol) dissolved in 5 mL of DMF. The reaction was performed in a 50-mL three-necked round-bottomed flask equipped with a reflux condenser, addition funnel, a gas outlet tube, and a magnetic follower. The vessel was heated by immersion in an oil bath in turn heated on an IKA magnetic stirrer hot plate equipped with a PT-100 probe with Fuzzy logic for self-optimising temperature control. Anhydrous copper (II) chloride (1.7 g, 13 mmol) in *N*,*N*-dimethylformamide (20 mL) was then added. Upon this addition, the reaction solution turned from the initial green copper (II) chloride colour completely black as nitrogen was evolved. Generally, gas evolution was complete within 10 min following the addition of the amine. After complete gas evolution the product was analysed by GC giving a conversion by area analysis of 40−49%. GC−MS spectra were also obtained and showed concordance.

2-Chlorotoluene was prepared and analysed as above from *o*-toluidine (0.1 g, 1.1 mmol) in *N*,*N*-dimethylformamide (0.5 mL), isoamyl nitrite (0.35 mL, 2.6 mmol), and anhydrous copper (II) chloride (0.17 g, 1.3 mmol) in *N*,*N*-dimethylformamide (2 mL).

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Reaction Monitoring. Optical monitoring was performed on an inverted microscope (Leica DMIL: Leica Microsystems Ltd, Milton Keynes, U.K.) with a CCD camera (SONY, CCD XC-999P) mounted onto the microscope and connected to a TV/VCR (Samsung/Panasonic). Transformation was monitored using a Hewlett-Packard (HP) 6890 capillary gas chromatograph (GC) utilising a HP Innowax stationary phase. Samples were introduced using a HP 6890 autosampler and autoinjector array to minimise operator errors. Samples were analysed without further purification by comparison to spiked standardised solutions (Lancaster Synthesis Ltd, Morecambe, U.K.). Traces were accumulated over a 42-min period and displayed using HP Chemstation software. The LabRam Infinity Raman microscope (Jobin Yvon Ltd. Middlesex U.K.) consisted of a 632-nm excitation laser, an inverted microscope, and a 50×/0.5 numerical aperture objective. The microfluidic reactor was secured to an *XY* translation stage and aligned with the excitation beam. Spectra were accumulated over a period of 30 s and displayed using Labspec V 4-02 software (Jobin Yvon Ltd., Middlesex, U.K.) running on a Pentium computer.

Conclusions

The application of microfluidic reactor technology to multistage reactions has been demonstrated. Utilising a continuous flow methodology the advantages of microscale reactors were illustrated by the intrinsically safe anhydrous diazotisation and chloro- and hydro-dediazonation of a variety of simple arenes, resulting in increased yields over those from similar reactions undertaken on a traditional scale. 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 the industrial route.

The utility of online optical detection using Raman spectroscopy has also been demonstrated for the first time in microfluidic reactor systems. Reaction monitoring was undertaken in real time with data acquisition rates shown to be ideally suited for on-line reaction feedback and control. The advantages of on-line monitoring over traditional off-line GC monitoring and the advantages of on-chip rather than capillary monitoring were elucidated.

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Supporting Information Available

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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