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Peter Styring [a]

[a] Department of Chemical and Process Engineering, The University of Sheffield, Sheffield, UK

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TOWARDS LIQUID CRYSTAL SYNTHESIS USING HIGH THROUGHPUT AND MICRO REACTOR TECHNOLOGIES

Peter Styring
Department of Chemical and Process Engineering,
The University of Sheffield, Sheffield, S1 3JD, UK

While many areas of chemistry, including pharmaceuticals, materials and fine chemicals, have embraced high throughput technologies, the field of liquid crystals has not. This is surprising, as the ability to screen large numbers of homologues and analogues in a short space of time is one of the rate-limiting steps in the development of new liquid crystalline materials. Here, the role of chemical micro reactors (CMRs) in the field of synthetic organic chemistry will be reviewed in light of their potential application in liquid crystal synthesis.

Keywords: EOF; liquid crystals; micro reactors; synthesis

INTRODUCTION

Over recent years the role of high throughput synthesis has achieved an increasingly important role in organic synthesis, particularly in pharmaceutical and fine chemicals research. However, a review of the literature reveals that this technology has not until now been adopted by research groups working in liquid crystal synthesis. High throughput chemistry, or parallel synthesis, can be used to routinely synthesise vast libraries of new materials and is particularly suited to the study of homologues and analogues of a 'lead' compound that are prepared under identical conditions [1]. In order to understand how high throughput synthesis can enhance the output of the liquid crystal chemist it is first appropriate to perhaps examine the subject and how it differs from combinatorial chemistry.

One of the main areas of confusion is the distinction between high throughput chemistry and combinatorial chemistry. In must be stressed that the two are not the same. *Combinatorial Chemistry*, as the name

Corresponding author. E-mail: p.styring@sheffield.ac.uk

suggests, involves mixing a diverse range of reactants to produce a mixture of products and the mixture as a whole is screened against a particular property [2]. In order to increase the diversity of products in a multi-step synthesis, the method called 'split and mix' can be used. This can be illustrated as follows. If reactant **A** and **1** produce compound **A1**, then a mixture of **A**, **B**, **1** and **2** will produce compounds **A1**, **B1**, **A2** and **B2**. Assuming that this produces a homogeneous mixture then this can be split into two equal portions that are further reacted with reactants **L**, **M** and **N** and **X**, **Y** and **Z** in separate reaction vessels. The resulting mixture will then be composed of products: (**A1L**, **A1M**, **A1N**, **B1L**, **B1M**, **B1N**, **A2L**, **A2M**, **A2N**, **B2L**, **B2M**, and **B2N**) and (**A1X**, **A1Y**, **A1Z**, **B1X**, **B1Y**, **B1Z**, **A2X**, **A2Y**, **A2Z**, **B2X**, **B2Y**, and **B2Z**). So in only two reaction steps, 24 new products have been formed. However, these are in a mixture that must either be separated or assayed. As the properties of a liquid crystal cannot be suitably assayed in a mixture, combinatorial chemistry is not appropriate. *High Throughput (HTP) or Parallel Synthesis* on the other hand involves the rapid synthesis of single component products either in sequence (*series*) or in parallel. In parallel synthesis the same reaction is performed on a large number of reactants, each contained within separate reactors, at the same time. Typical parallel syntheses involve 12, 24, 48 or 96 simultaneous reactions, each giving a isolatable product which can then be screened. High throughput synthesis encompasses parallel synthesis but can also be used in serial mode where continuous flow, rather than batch, reactors are used. In this case a reaction is performed with the reaction solution flowing through a reactor for a given time period after which the reactor is flushed with solvent and a new reaction mixture introduced. This can be repeated and continued for a diverse range of substrates and the reactor outflow collected by autosampler before each solution is worked up, typically using parallel purification techniques, purified and characterised.

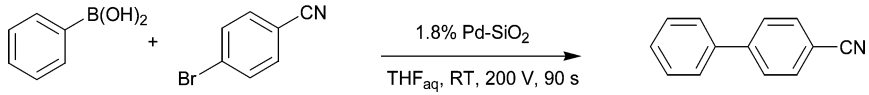
Chemical micro reactors (CMRs) are an emerging technology [3,4] that represent a step change or *paradigm* shift in the way that synthetic chemistry is carried out. CMRs are attractive for a number of reasons that include reduced waste, precise control over reaction conditions and product distribution and the ability to perform the synthesis at the point of need [3]. Micro reactors are continuous flow reactors. That is to say that the reaction solution is the mobile phase that passes through a reactor tube either by applying a pressure or through applying a concentration gradient to give electroosmotic flow (EOF)[5]. The dimensions of micro reactors differ considerably from 200 μm to a few tens of μm. However, even over this range of dimensions the Reynolds number of the system is low (significantly <2000) and so laminar (non-turbulent) flow will be observed. Therefore, without the influences of any other outside forces, the reaction

will occur solely as a result of diffusive mixing between the laminar flows. A number of variations on CMR design have been reported in the literature based on silicon, polymer, or glass substrates. In the case of EOF, a substrate must be used that possesses a zeta potential at the surface. This is most usually borosilicate glass. Channels are produced in a glass plate by photolithographic and wet etching techniques and a top plate containing fluid reservoirs attached through thermal bonding [6]. EOF is produced using platinum or gold electrodes that are placed in the reservoirs and applying an electric potential between them. In the case of pressure driven flow syringe pumps, and sometimes peristaltic pumps, are the driving forces used.

MICRO REACTORS IN THE SYNTHESIS OF LIQUID CRYSTALS

The use of chemical micro reactors in synthetic chemistry is an emerging technology, driven primarily by the pharmaceuticals industry where rapid discovery of new commercial products is essential. However, many of the techniques already developed in pharmaceuticals can be readily transposed into liquid crystal synthesis. If we look at the core synthetic 'Toolkit' for the liquid crystal chemist it is not that dissimilar to the pharma chemist: metal catalysed or non-catalytic C−C bond-forming reactions; alkyl- and acylations; condensation reactions; hydrogenations, selective oxidations. At the present time this toolkit is still in development and so only a small literature is available. In order to illustrate the versatility of micro reactors in the synthesis of liquid crystals it is necessary to consider in the first instance only the core reactions, not the fine detail. For example, in the synthesis of polyaromatic liquid crystals the key feature is the formation of an aromatic C−C sigma bond, irrespective of the substituents on the core. Therefore, only the enabling 'Toolkit' of reactions appropriate to liquid crystals will be considered in this paper. The intention is to expose liquid crystal chemists to this new technology and therefore encourage more people to embrace it and widen its scope.

Some of the early CMR work in organic synthesis looked at the much favoured Suzuki-Miyaura coupling reaction in which an aryl halide is oxidatively added to a Noble metal catalyst, usually a palladium(0) complex or a palladium(II) precursor complex, and then coupled with an appropriate aryl boronic acid. The pre-requisite for this reaction to work effectively is that each of the coupling organic substrates must be aromatic. A typical stirred batch reaction that is carried out in a chemistry laboratory uses a dilute solution of the organic substrates in a suitable solvent, typically dimethoxyethane (DME), and a base such as sodium carbonate together with the palladium catalyst (e.g. tetrakis(triphenylphosphine)palladium



SCHEME 1 Synthesis of 4-cyanobiphenyl in a CMR under EOF.

(0)). The mixture is then heated to reflux and vigorously stirred for anything from 8 to 72 hours depending on the particular substrates and catalyst. Yields can vary considerably and the activity of the catalyst can be affected by the nature of the substrates. One question that arises is how efficient is the mass transfer in such a reaction? The answer is that it is usually poor because the reactor is generic, usually a round-bottomed flask, and so not optimised for the reaction. It is very rare for a chemist to state the speed at which the reaction was stirred let alone the design of the stirrer or impeller used. Therefore, certainly in dilute solutions used, the reactants barely see each other. One of the benefits of a CMR is that we are able to accurately control the spatial and temporal location of the reactants, and because of the small dimensions of the capillary micro channels we have the opportunity to keep reactants in close proximity while they are within the reactor section. As a case study we have looked at the synthesis of 4-cyanobiphenyl (Scheme 1) using a Suzuki-Miyaura reaction in a 'T'-channel CMR [7]. Solutions of phenylboronic acid and 4-bromobenzonitrile, each 0.1 M in 25% aqueous THF, were introduced into the linear reactor section of the 'T'-chip under EOF, with an applied electric field gradient of 154 V cm^{-1}(15 kV m^{-1}), from each side of the T respectively (Fig. 1). The collection reservoir was grounded to produce the gradient. The linear reactor section was packed with a silicate frit containing the catalyst, 1.8% palladium metal on silica. A flow rate of 0.8 μL min^{-1} was

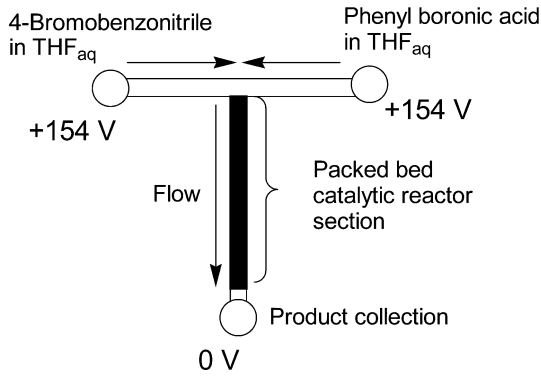


FIGURE 1 Schematic diagram of the 'T'-chip reactor channels.

achieved at this field gradient over the total catalytic reactor volume of 1.19 μL. This gave a residence time, and therefore reaction time, of the reagents over the catalyst of 90 s. It should be noted that no base was added to the system and the synthesis was carried out at room temperature, both of which are in contrast to the batch reaction. Over replicate runs under the same conditions, the yield of 4-cyanobiphenyl as determined by GCMS (M+ 179 Da) was $67 \pm 7\%$. The same reaction carried out in batch, without added base and at both ambient temperature and reflux, using a magnetic follower and a stirring rate of 500 rpm produced no product. When aqueous sodium carbonate was added under conditions of reflux, only 10% conversion was achieved after 8 hours. The conversion could be increased to around 65% but only on constant reflux for 72 hours. Batch reactions were carried out in duplicate under identical reaction conditions. This reaction not only illustrates the importance of micro reactors in achieving good mass transfer but also the influence of the EOF. It has been proposed that the electric field is responsible for the generation of the basic conditions necessary for the reaction to proceed through partial hydrolysis of the water at the Pd-SiO_2 surface: precisely where it is required. This fact is represented in the catalytic cycle proposed for the reaction carried out under EOF (Fig. 2). In order to appreciate the benefit from such a reaction in a CMR it is necessary to consider normalised yields and residence times. If 0.1 mol of each reagent solutions is used in batch to give 10% yield in 8 hours, then 0.01 mole of product is formed in that time. However it is the minor component of the reaction mixture and there is the potential to lose 90% of the starting materials during the work-up.

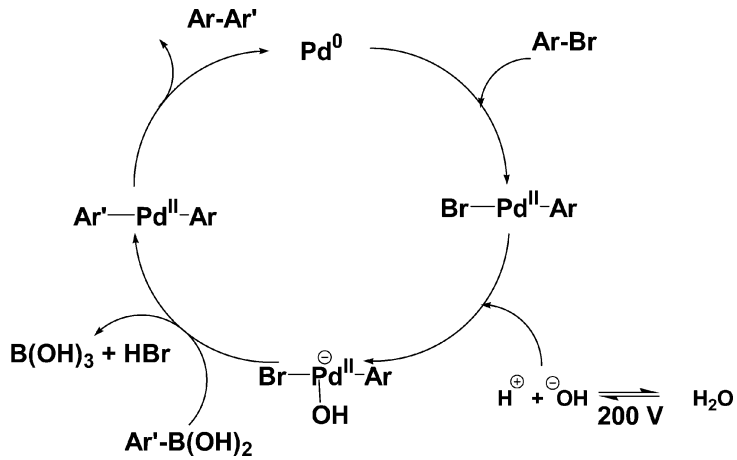
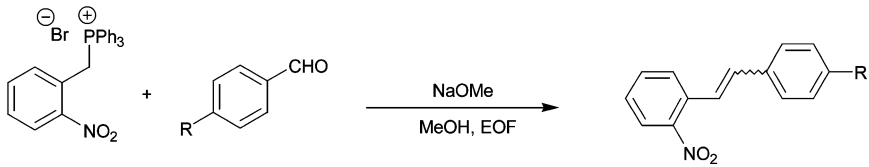


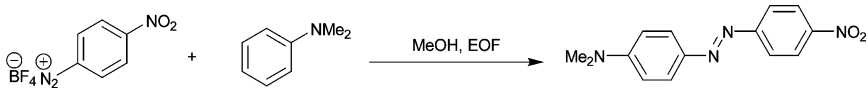
FIGURE 2 Catalytic cycle for the Suzuki-Miyaura reaction under EOF.

In reality such losses would not be tolerated and the reaction would be allowed to proceed until maximum conversion could be achieved. However, there is a penalty in terms of additional reaction time on process economics: longer reaction times tie up important apparatus and have increased energy cost. The rate of production of product in the batch processes given here is then 2×10^{-5} mol min^{-1} taking the production over 8 hours or 1.5×10^{-5} mol min^{-1} taking the production over 72 hours. These can be considered similar within experimental error. The production rate using a CMR is in this case lower: 6×10^{-8} mol min^{-1}: equating to a 300 times smaller amount of product. However, assuming complete recovery, the batch process will give 1.8 g of product, which is much more than is required for initial screening, and there will be considerable waste. The CMR process, over eight hours, will give 6 mg for a single channel reaction over the same period of time, however if scaled out to 20 parallel channels the recovered product will weigh 120 mg, more than enough to perform a complete chemical, structural and thermal analysis.

Prior to the use of metal catalysts to form C–C bonds, the Wittig reaction was typically used to introduce a double bond into an organic molecule and diazo couplings were used to introduce aryl-aryl single bonds. In the Wittig reaction a ylide, formed by the deprotonation of a phosphonium bromide, reacts with an aldehyde gives a oxaphosphetane intermediate that eliminates water to give an alkene motif in the product. The stereochemistry of the oxaphosphetane intermediate determines whether the *cis* or the *trans* alkene is formed. Chemistry performed in a CMR [8] (Scheme 2) shows it is not only possible to form alkenes using Wittig chemistry under the influence of EOF in yields of greater than 60%, but also that the electric field strength plays a major role in the stabilisation of the betaine intermediate and hence the stereochemistry of the alkene product [9]. At low field gradients the *trans* (*E*) isomer is formed in excess while at high fields the *cis* (*Z*) isomer predominates. A number of reasons have been postulated to account for this observation, including a field induced internal dipolar alignment at high fields to give the *E*-oxaphosphetane intermediate; or the difference in linear velocity of the reagents through the channel as a function of applied field [9]. As the field gradient is increased, the linear



SCHEME 2 Wittig reaction in a CMR under EOF.

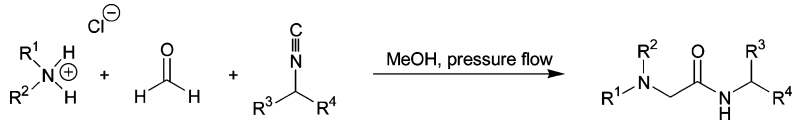


SCHEME 3 Diazo coupling reaction in a CMR under EOF.

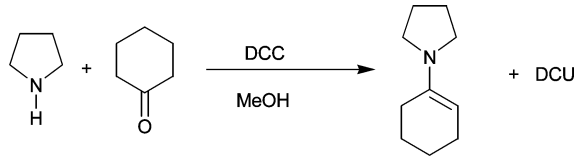
velocity increases and therefore the residence time on the reactor is small. The kinetically stable *Z*-isomer of the oxaphosphetane forms (kinetics limited) which passes through the reactor before it can rearrange to the thermodynamically stable *E*-form. At low field gradients the residence time is long so rearrangement can occur to give the thermodynamically stable *E*-isomer (enthalpy of formation limited). The diazo coupling reaction has been shown to proceed in 37% conversion when carried out in methanol (polar, protic) solution in a glass chip under EOF [10] (Scheme 3). When a polar aprotic solvent such as acetonitrile was used the conversion was substantially reduced.

Other condensation reactions have been reported by a number of authors, many of which can be applied to liquid crystal syntheses. Mitchell *et al*. have reported the serial synthesis of *β*-aminoamide derivatives using an Ugi-type reaction on a micro reactor [11] (Scheme 4). At the present time this has been performed solely to demonstrate SYNTAS (synthesis-total analysis system) technology but can be seen as an enabling technology to the production of diversity-driven liquid crystal libraries. Sands *et al*. have demonstrated the synthesis of enamines [12], important reaction intermediates, using CMR technology. In the reaction, cyclohexanone and DCC (drying agent) in anhydrous methanol was contacted with pyrolidine in anhydrous methanol under EOF and the product stream from the reactor collected and analysed by GCMS. Although the data are preliminary it appears that a rate enhancement is observed in the CMR system over the batch process. A conversion of 42% to the enamine was observed without the need to add a base (Scheme 5).

From the early days of HTP chemistry, there has been a drive from the therapeutics viewpoint to produce proteins (polypeptides). These may well be of interest to the lyotropic community as it is possible using these techniques to readily prepare unnatural polypeptides that may be of potential



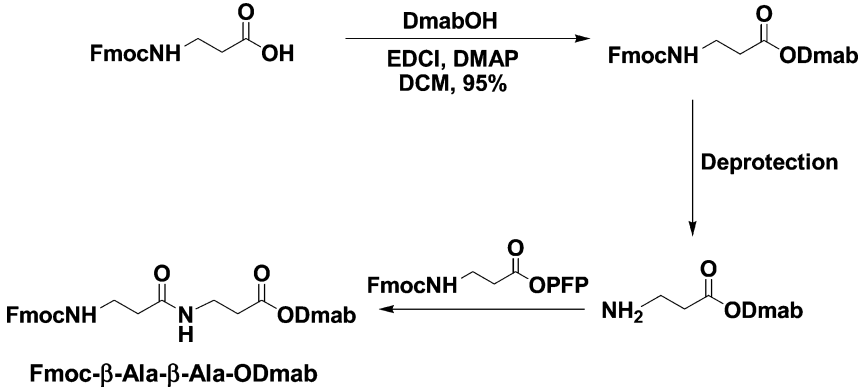
SCHEME 4 Ugi-type reaction using isocyanates in a CMR under pressure driven flow.



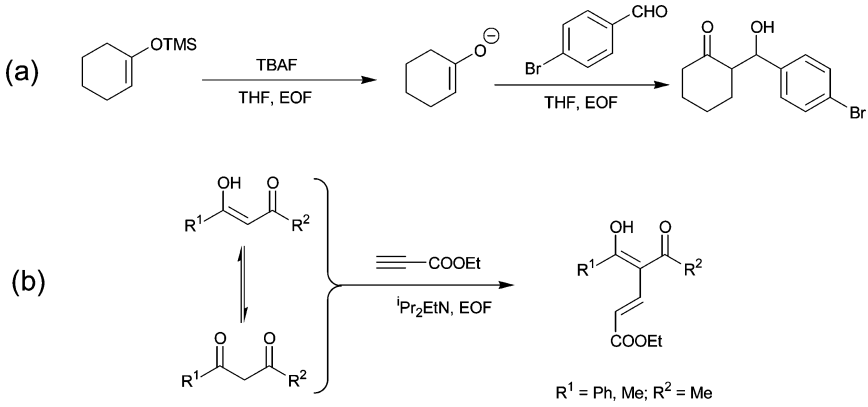
SCHEME 5 Enamine synthesis in a micro reactor using EOF under anhydrous conditions.

interest. However, the procedure reported by Watts *et al.*, is of interest to the general synthetic chemist in that it combines condensation chemistry with protection and deprotection chemistry on a chip [13]. In the reported procedure, an unnatural β-dipeptide was prepared based on β-alanine. One method used the coupling of the pentafluorophenyl ester activated Fmoc-β-alanine with the Dmab ester protected β-alanine in DMF under EOF. The dipeptide formed in quantitative yield, a considerable improvement over the conventional batch process that gave a conversion of only 40–50%. Further studies also revealed the use of both Fmoc and Boc in protection/deprotection strategies and their utility in CMRs (Scheme 6).

Wiles *et al.* have demonstrated the potential of EOF driven flow in CMRs to perform carbanion chemistry. In one example, a silylenol ether was treated with *tert-n*-butylammonium fluoride (TBAF) in THF to give the enolate intermediate that reacted with 4-bromobenzaldehyde to give the β-hydroxyketone (Scheme 7(a)) in quantitative yield [14]. In a further study, 1,3-diketones were enolised under EOF using an organic base and these were reacted with α,β-unsaturated esters to give the Michael addition



SCHEME 6 Peptide synthesis in a CMR under EOF using protection-deprotection strategies.

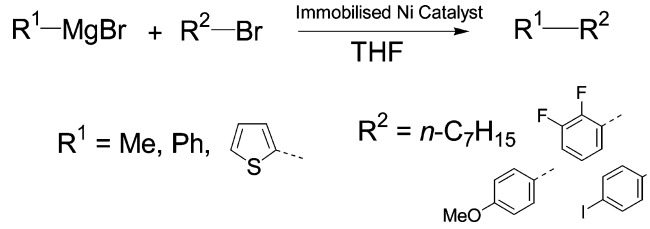


SCHEME 7 Carbanion chemistry in a CMR under EOF.

product as shown in Scheme 7(b). Continuous flow methods under EOF on a glass chip gave low conversions, typically 15%. However, by using stop-flow techniques to increase the residence time on the reactor conversions became quantitative [15].

All the CMRs discussed so far are based on the lithographic-etch techniques to give reactors with μL volumes. In order to scale the reaction to synthetic quantities it is possible to scale-out through parallelisation of the individual channels. Another way is to build CMRs based on single, larger micro capillaries interfaced by standard HPLC connections. O'Sullivan *et al*. have reported the use of a polymer-supported nickel catalyst packed into a capillary as an effective system for the Tamao-Kumada-Corriu coupling reaction [16]. The reactor operates in pressure flow mode using a syringe pump against the packed bed catalysts. The 'Kumada' coupling reaction has an advantage over the Suzuki coupling in that there is no restriction in the choice of organic substrate. The Suzuki coupling requires unsaturated substrates in all cases, however the Kumada coupling uses Grignard reagents and organohalides in any hybridisation; sp, sp^2 or sp^3. The consequence is that the Kumada reaction can be used in lateral sp^3-hybridised chain addition as well as modification of the liquid crystal core. Some examples are given that show how the Kumada reaction can be used in the synthesis of pro-liquid crystalline structures.

Kumada reactions were performed in glass or polypropylene capillaries (OmniFit) of 1 and 2 mm internal diameter respectively. One of the targets was the synthesis of a substituted biphenyl core, therefore 4-bromoanisole was reacted with phenyl magnesium bromide in THF to give 4-methoxy-biphenyl (Scheme 8). The reaction was carried out in a stirred batch reactor at room temperature to give the product in 71–73% yield after

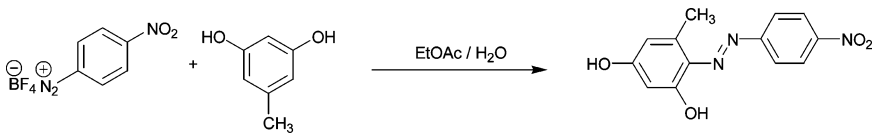


SCHEME 8 'Kumada' reaction in a CMR under pressure flow.

24 hours. Kinetic studies showed the reaction to be first order in respect of the organobromide with an observed rate constant of 2×10^{-5} s^{-1}[17]. When the reaction was performed in the pressure driven CMR at a linear flow rate of 33 μL min^{-1} 60% conversion was achieved with a residence time on the catalyst of only 50 s. This gave a continuous flow observed rate constant of 2×10^{-2} s^{-1}, which represents a three orders of magnitude rate enhancement. In order to test the feasibility of the Kumada reaction in a micro reactor with respect to alkylation (chain addition) reactions, *n*-1-bromoheptane was reacted with phenyl magnesium bromide to give *n*-heptylbenzene in 40% conversion. While this is relatively low, it is a single step procedure and therefore better than more conventional multi-step procedures that incur losses at each step. The method is also tolerant to sulfur heterocycles as exemplified by the reaction of 4-bromoanisole with thiophenyl magnesium bromide in THF to give 2-(4-methoxyphenyl)thiophene in 71% yield.

Pressure driven flow has been used by Hisamoto *et al*. to prepare substituted azo dyes [18], similar in structure to many early liquid crystals, using phase transfer conditions on a chip (Scheme 9). An aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate was contacted with a concurrent parallel flow of 5-methylresorcinol in ethyl acetate. Analysis of the reactor outflow showed the conversion to the product to be quantitative.

Other chemistries such as hydrogenation, dehydration, oxidation and fluorination reactions have also been investigated, however these have all been performed using gas phase reagents and therefore are not at



SCHEME 9 Diazo coupling reaction to give an azo dye in a CMR under pressure flow.

this point in time applicable to the synthesis of liquid crystals [3,19,20]. However, research is continuing into the effect of two phase flow in liquid-gas reactions in CMRs to achieve such reactions in liquids under both homogeneous and heterogeneous catalytic conditions.

CONCLUSIONS

Chemical micro reactors have been used to demonstrate their application to a number of organic chemical reactions. While still a technology in its infancy, it is clear that it will have a significant impact on the way in which new compound discovery is performed. There are inherent savings to be made in both discovery and production through the use of this new technology, through reduced reagent consumption and transportation costs, increased reaction efficiency and process safety, and through the ability to scale out identical reactions in parallel. While the technology has been developed for use in the pharmaceuticals industry, it is clear that there is also a market to be exploited in liquid crystals discovery. The examples given in this paper are illustrative and aim to give the reader an idea of the 'toolkit' that is developing and which is appropriate and applicable to the synthesis of liquid crystals.

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