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Solid-Supported Continuous Flow Synthesis in Microreactors Using Electroosmotic Flow

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Abstract:

This paper reports the fabrication of a microreactor suitable for use with supported reagents. We demonstrate that the electroosmotic flow can be used to move the reagents over a solid-supported catalyst bed. It is demonstrated that it is important that the support should not swell in organic solvents to obtain reproducible flow, and it is shown that silica supports fulfill this criteria. Silica-functionalised piperazine is used in a variety of Knoevenagel reactions to give the product in high conversion.

Introduction

Over the past five years there has been a rapid growth in the development of microreactor technology exploiting the technique of electroosmotic flow (EOF).[1] The application of electroosmotic flow instead of hydrodynamic pressure overcomes two most commonly faced problems in continuous flow reactors utilising solid-supported synthesis. First, technical problems such as bypassing of the reagents or pressure drop are avoided, as unlike pressure-driven systems EOF is uniform along the channel. A practical consequence of this is that very small particles can be used in the system, as EOF unlike pressure-driven systems is independent of particle size. This can result in greater surface-to-volume ratios and increases the number of reactive sites on the solid support. Second, very low flow rates can be achieved which make the synthesis procedure much more efficient. Such low flow rates cannot be reproducibly achieved within a pressure-driven device when using a syringe pump. Recent research has shown that a vast number of solution phase reactions such as diazo synthesis,[2] Michael additions,[3] aldol condensations,[4] heterocyclic synthesis,[5] and multistep peptide synthesis[6] may be performed within microreactors using this technique; these and many other examples have been discussed in several reviews.[7]

In comparison, very few publications have reported solution phase organic synthesis in microreactors using solid-supported reagents or catalysts, as the challenge for some time has been to develop microreactors suitable for use with supported reagents. Skelton reported a device for the Suzuki reaction.[8] However, as a Pd catalyst was used, it was very easy to position the catalyst within the device before the top block was thermally annealed; in fact the high temperature used to effect the bonding of the device probably further activated the catalyst. Similarly, McCreedy[9] has reported a reactor that effected the dehydration of alcohols using a sulphated zirconia catalyst. As a result of using alcoholic solvent systems, it was possible to use a microreactor fabricated from a PDMS top block, onto which the catalyst had been impregnated; however this type of approach would not be feasible when organic solvents are required.

Since the pioneering work of Merrifield,[10] solid supported synthesis has been an important technique in organic chemistry. In particular, the use of solid supported reagents in solution phase organic synthesis has been of enormous importance.[11] The driving force behind this research has been the rapid expansion in high-throughput parallel synthesis and the ever increasing need to simplify workup and reaction procedures. Among different solid supported reagents that have been used, supported catalysts are particularly convenient as excess immobilized catalyst can be used to drive reactions to completion. More recently it has been reported that solid supports suffer less physical damage in flow systems compared to batch reactions where vigorous stirring is required.[12]

Here we report a novel method to perform efficient and reliable solid supported synthesis in a continuous flow microreactor. This technique combines the advantages of continuous flow synthesis and microreactors. In this communication we report an example of using electroosmotic flow in a microreactor to perform Knoevenagel reactions.

Experimental Section

The microreactor used for solid supported reactions was fabricated by Micro Chemical Systems from borosilicate glass using standard fabrication methods developed at Hull.[13] The device was fabricated from a top block and two etched

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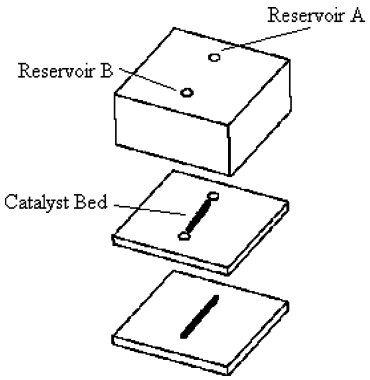


Figure 1. **Schematic of the microreactor.**

plates, which enabled a deeper catalyst bed to be achieved (Figure 1). The channels were 130 μm wide and 50 μm deep, and the catalyst bed was 800 μm wide, 100 μm deep, and 10 mm in length. An in-house LabVIEW program was used to set and monitor the voltages that were applied to platinum electrodes that were placed in the reagent reservoirs (power supply was built by Kingfield Electronics, Sheffield, UK).

All microreactions were performed over a period of 5 min at room temperature to ensure that sufficient volume of product was generated for analysis. Reaction products were determined by GC−MS (Varian GC (CP-3800) coupled to a Varian MS (Saturn 2000), 30 m CP-Sil 8 column (Phenomenex), injector temperature 200 °C, helium flow rate 1 mL min^{-1}, oven temperature 60 °C for 1 min then ramped to 270 °C at 25 °C min^{-1}). Reaction products were determined via the comparison of retention times and mass spectra with those obtained from a series of synthetic standards (see below). Analysis of the crude reaction mixtures by GC−MS enabled the proportion of product to be determined with respect to residual starting material.

Synthesis of Supported Piperazine. 4-Benzyl chloride functionalized silica gel (1.00 g, 1.30 mmol) and piperazine (0.67 g, 7.80 mmol) were heated to reflux in the presence of potassium carbonate (0.54 g, 3.90 mmol) in acetone (25 mL) for 5 h. The product was filtered under vacuum and washed with water and acetone (2 × 25 mL) to give a silica-bound piperazine. Elemental analysis showed 0.7 mmol/g presence of piperazine moiety.

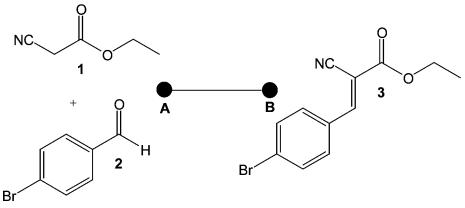
Ethyl 3-(4-bromophenyl)-2-cyano acrylate 3: *m*/*z* (EI) 281 ($M^+ + 1$, 90%), 280 (45), 279 (100), 251 (25), 200 (20), 154 (10), 127 (25), 100 (20) and 76 (20); GC−MS retention time $R_T = 9.5$ min.

Ethyl 2-cyano-3-phenyl acrylate 6: *m*/*z* (EI) 202 ($M^+ + 1$, 70%), 201 (100), 172 (80), 156 (90), 128 (75), 102 (55), 77 (50), and 51 (50); GC−MS retention time $R_T = 8.3$ min.

Ethyl 3-(3,5-dimethoxyphenyl)-2-cyano acrylate 7: *m*/*z* (EI) 262 ($M^+ + 1$, 20%), 261 (100), 189 (55), 161 (25), and 77 (10); GC−MS retention time $R_T = 10.2$ min.

Ethyl 3-(4-benzyloxyphenyl)-2-cyano acrylate 8: *m*/*z* (EI) 308 ($M^+ + 1$, 5%), 307 (20), 91 (100), and 65 (20); GC−MS retention time $R_T = 15.1$ min.

Scheme 1. **Microreactor manifold for Knoevenagel reactions**



Scheme 2. **Immobilization of piperazine**

Table 1. **Effect of field strength and concentration on conversion to 3**

	voltage (V)		
concn (M)	200	300	400
0.5	48 ± 3	25 ± 2	23 ± 1
1.0	39 ± 3	52 ± 6	43 ± 9
2.0	92 ± 2	90 ± 5	90 ± 5

Results and Discussion

In the first instance, the microreactor illustrated in Figure 1 was packed with piperazine on Merrifield resin, Tentagel, or Argopore, and the microreactor was primed with acetonitrile. Using the reaction manifold illustrated in Scheme 1, the preparation of ester **3** was investigated within the microreactor; a premixed solution of ethyl propiolate **1** and 4-bromobenzaldehyde **2** (40 μL, 1.0 M) in anhydrous MeCN was placed in reservoir A, and the reaction products were collected in anhydrous MeCN in reservoir B.

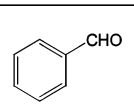
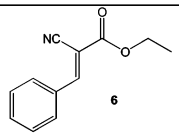
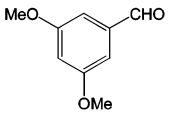
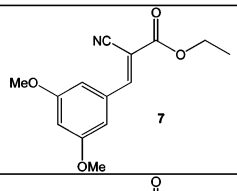
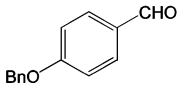
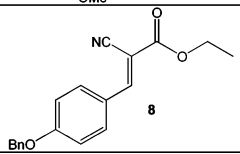
However it was found that the polymer became more and more swollen with time causing irreproducible flow rates, which resulted in variable conversions, which was unsatisfactory. To circumvent this problem, it was proposed that a support that does not swell in organic solvents is required when using microfluidic systems, and consequently piperazine was immobilised onto silica, as this material has a broad range of solvent compatibility and suffers minimal swelling in a range of organic solvents. Piperazine was immobilised onto benzyl chloride functionalised silica gel **4** to give product **5** containing 0.7 mmol/g piperazine by CHN analysis (Scheme 2).

The catalyst bed was subsequently packed with piperazine functionalized silica **5** and primed with acetonitrile to remove air bubbles from the device. The reaction of ethyl cyanoacetate **1** and 4-bromobenzaldehyde **2** in acetonitrile to produce ethyl 3-(4-bromophenyl)-2-cyanoacrylate **3** was then investigated using the methodology described above.

The reaction was investigated at a range of concentrations and field strengths (i.e., flow rates) to optimise the conditions. Each reaction was repeated 5 times, and the average conversion for each set of reactions is shown in Table 1.

Table 1 clearly shows that by increasing the concentrations of the starting materials the conversions correspondingly increase. This increase in conversion was expected as reagents have a greater chance to interact with the im-

Table 2. **Knoevenagel reactions using other aldehyde derivatives**

Aldehyde	Product	Conversion (%)
	 **6**	82±2
	 **7**	83±4
	 **8**	51±7

mobilized base. Furthermore, as expected, as the field strength is reduced the conversion to product increases. We propose that the reduced field strength results in a reduced flow rate, which increases the residence time of the reaction resulting in a higher conversion.

The results clearly show that the microreactor is able to generate reliable and reproducible data, as the level of error is within an acceptable range. The data show that greater conversions can be achieved by increasing the concentration. As would be predicted, increasing the time of the reaction to up to 20 min had no effect on the conversions which illustrates that the system could be used in continuous flow mode in a "scaled out" device to produce larger quantities of product.

Evaluation of Analogous Reactions. After optimizing the condition of the reaction, a series of other Knoevenagel reactions using ethyl propiolate **1** were conducted at 2.0 M concentration using other aldehydes. The results are summerized in Table 2. The lower conversion for the 4-benzyloxybenzaldehyde derivative can be attributed to its lower solubility which makes it difficult to work with a 2.0 M solution of this compound.

Conclusion

It has been shown for the first time that EOF can be used to perform continuous flow, solid supported synthesis in a microreactor. Using EOF to move reagents over a solid phase can be very advantageous in flow systems, as very low flow rates are achievable. In comparison, results of pressure driven systems (not shown here) were found to be highly irreproducible. A practical consequence of this is that very small particles can be used in the system, as EOF unlike pressure-driven systems is independent of particle size. The small particle size can result in a greater surface-to-volume ratio thus increasing the number of reactive sites on the solid support. The reaction also seems to happen much quicker and at lower temperatures when compared to batch reactions (5 min vs 2 h). We propose that this methodology significantly increases the versatility of microreactor synthesis.

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