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SCIENCE DIRECT
Tetrahedron
Tetrahedron 60 (2004) 8421–8427

# An investigation into the use of silica-supported bases within EOF-based flow reactors

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Received 6 April 2004; revised 8 June 2004; accepted 1 July 2004

**Abstract**—Using a series of silica-supported bases, we demonstrate the synthesis of eight condensation products within an EOF-based flow reactor; in all cases, high yields (>99%) and product purity are obtained.


## 1. Introduction

Increased demand for the rapid preparation of small molecule libraries has led to renewed interest in the development of clean and efficient techniques for the synthesis of organic compounds. With this in mind, the miniaturisation of reaction technology is of particular interest to the pharmaceutical industry, where long term objectives include the desire to perform multiple functions such as synthesis, detection, screening and biological evaluation within a single integrated device, resulting in an overall reduction in the time taken to discover new lead compounds and put them into production.[1] To date, numerous compounds have been successfully synthesised within micro fabricated devices with many groups demonstrating advantages over traditional batch techniques such as greater reaction control, leading to increased conversions, selectivities and reduced reaction times.[2] Although many groups have begun the task of transferring synthetic methodology from batch to micro reactors, few have addressed the problems associated with product purification in continuous systems.[3] In order to tackle these problems, we were interested in the use of solid-supported reagents.[4]

### 1.1. Solid-supported reagents

Compared to solid-phase techniques,[5] where reaction intermediates are immobilised and cannot be fully characterised until cleaved from the support, the use of solid-supported reagents means that reaction products remain in solution, enabling reaction progress to be monitored. As the technique couples the advantages of both solid and solution-phase synthesis, the use of solid-supported reagents means that excess reagent can be employed in order to drive the reaction to completion, while the reagent can be easily removed from the reaction mixture. With the obvious similarities to solid-phase synthetic methodology, polymers have found widespread use in the preparation of solid-supported reagents;[6,7] other materials however include zeolites,[8] clays[9] and silicas.[10] Unlike certain polymers, silica exhibits no swelling in organic solvents and is thermally, chemically and mechanically stable; consequently, its use as a support is becoming more widespread. Due to the non-porous nature of the support, functionalisation is limited to the surface and as a result, reaction rate is not limited by reagent diffusion whilst enabling controlled, reproducible loading. In order to prevent any undesirable adsorption of materials onto the silica, any unfunctionalised silanol groups are end-capped. With this in mind, we were interested in investigating the incorporation of silica-supported reagents for continuous synthesis in a miniaturised flow reactor.

### 1.2. Knoevenagel condensation

The Knoevenagel reaction is defined as the condensation of an aldehyde or ketone with compounds that possesses an active methylene group. The reaction is brought about using organic bases such as primary or secondary amines.[11] The active methylene groups employed include nitro, cyano and acyl groups and in most cases, two groups are required in order to provide sufficient activation. As Scheme 1 illustrates, the primary product formed is the unsaturated product although, in some cases, further reaction may take place with a second molecule of the activated methylene compound resulting in a Michael addition to afford the bis product. With careful selection of the starting materials, enantioselective[12] and diastereoselective[13] condensation

*Keywords*: Silica supported base; Knoevenagel reaction; Flow reactor.
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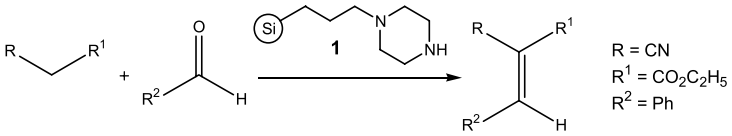
doi:10.1016/j.tet.2004.07.006




**Scheme 1.** General scheme illustrating the reaction of activated methylenes and aldehydes with a functionalised silica gel **1**.

products may be obtained. The main disadvantage associated with the Knoevenagel condensation is that the reactions do not proceed to completion and require purification to remove the organic base and its salt. Many alternatives exist, including acid catalysed condensations,[14] dry grind,[15] the use of microwave irradiation,[16] zeolites,[17] aluminium oxides[18] and the use of amino functionalised polymers[19] and silica gels.[20]

It was therefore proposed that by incorporation of a series of supported bases into a micro-fabricated device, that product purity could be increased while simultaneously maintaining the advantages associated with miniaturisation. Firstly, in order to compare the use of supported reagents within a flow reactor with traditional batch techniques, the reactions were initially performed in batch using both silica-supported and solution phase bases.

## 2. Results and discussion

As Scheme 1 illustrates, treatment of an activated methylene with a base **1** in the presence of an aldehyde, results in the preparation of an unsaturated product (Fig. 1).

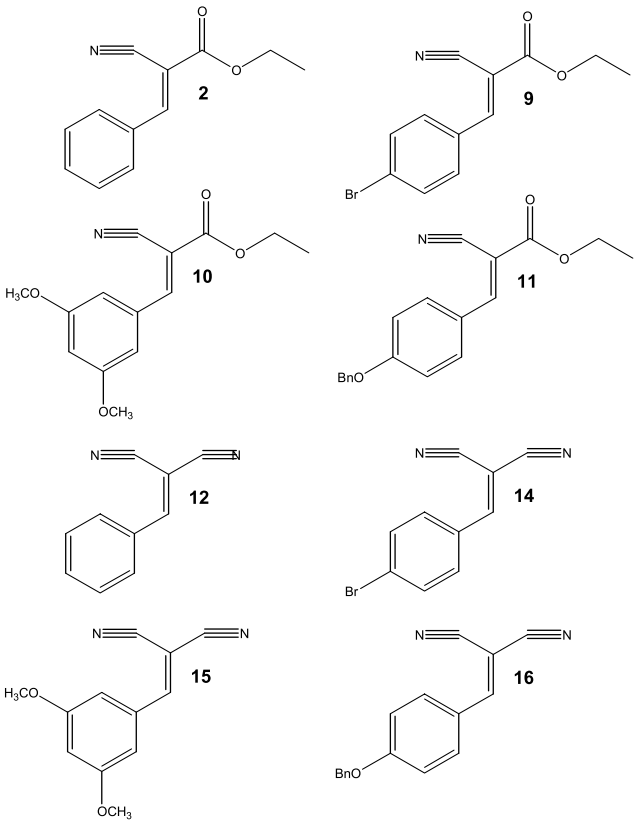



**Figure 1.** Synthetic targets for preparation in a miniaturised device.

Prior to investigating the incorporation of a silica-supported base within a flow reactor, using the preparation of 2-cyano-3-phenyl acrylic acid ethyl ester **2** as a model reaction, the rate of reaction was compared to a solution phase base at room temperature. As Figure 2 illustrates, compared to piperazine **3**, the rate of conversion is markedly reduced when 3-(1-piperazino)propyl-functionalised silica gel **1** is employed.

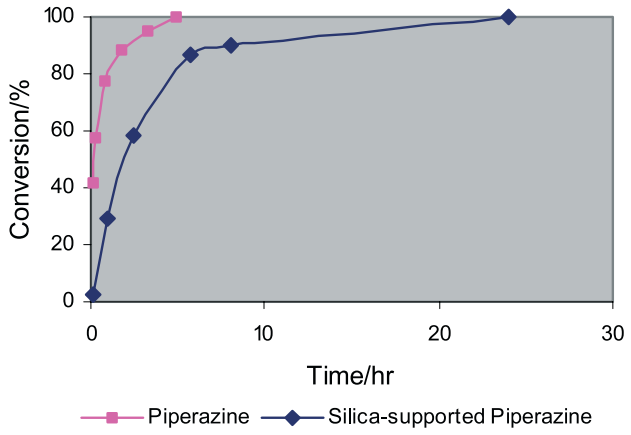



**Figure 2.** Graph illustrating the rate of conversion when employing solution-phase organic bases compared with solid-phase bases.

Having demonstrated the successful synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** using 3-(1-piperazino)propyl-functionalised silica gel **1**, the next step was to investigate reagent longevity. As Figure 3 illustrates, recycling the reagent results in a significant decrease in conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2**. As the reaction is base catalysed and the reagent is end-capped to prevent fouling, the increase in reaction time was attributed to a loss of reagent as a result of recycling. In order to confirm this, the reaction was again investigated

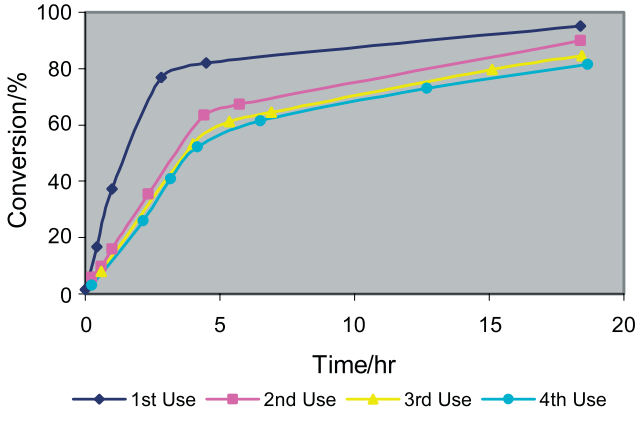



**Figure 3.** Graph illustrating the effect of recycling a solid supported reagent on the rate of conversion.

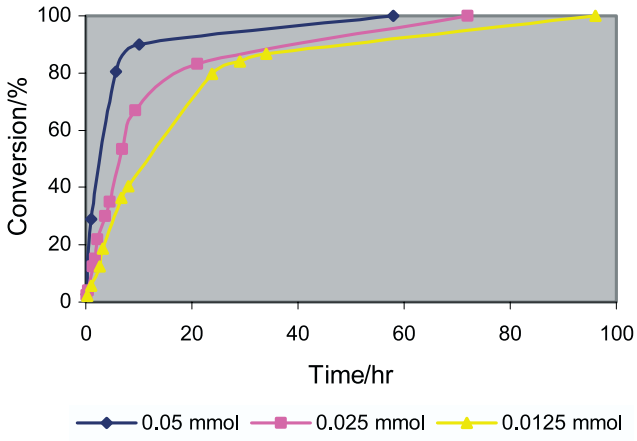



**Figure 4.** Graph illustrating the effect of base amount on the rate of conversion.

using varying amounts of 3-(1-piperazino)propyl-functionalised silica gel **1** (0.05–0.0125 mmol). As Figure 4 illustrates, as the quantity of base employed is decreased, the reaction time required increases, confirming the reduction in reaction rate is due to reagent loss. Having demonstrated the ability to recycle 3-(1-piperazino)propyl-functionalised silica gel **1**, the next step was to demonstrate its use in a micro fabricated device.

In order to evaluate the use of silica-supported reagents within an EOF-based system, a miniaturised flow reactor was investigated (Fig. 5). This approach not only enabled the reagents to be packed with ease but also provided a relatively inexpensive, versatile system. Although examples of pressure-driven systems have been reported within the literature, owing to its simplicity, the technique of electroosmotic flow (EOF) is demonstrated. The technique is advantageous as it is simple to use, requires no mechanical parts, enables reproducible pulse-free flow and most importantly, with respect to packed systems, generates minimal back-pressure.[21] As Figure 6 illustrates, when an ionisable surface such as glass, quartz or Teflon, comes in contact with a suitable solvent system, the surface is neutralised with a diffuse layer of positive ions from the bulk liquid. A proportion of the counterions are adsorbed onto the surface, resulting in the formation of an immobile layer, and the remaining positive ions form a transient

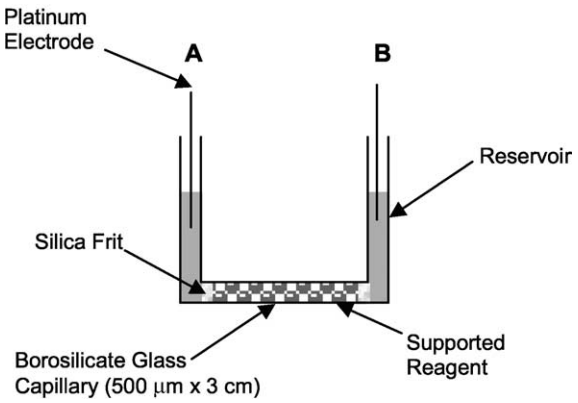



**Figure 5.** Schematic of the reaction set-up used for the evaluation of solid-supported reagents.

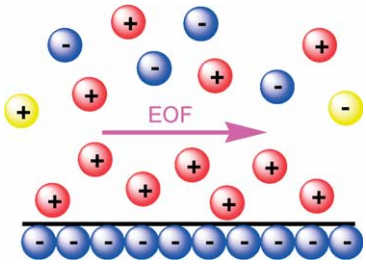



**Figure 6.** Schematic illustrating the principle of electroosmotic flow.

double layer. Application of an electric field causes the double layer to move towards the most negative electrode, inducing bulk flow within the microchannel.

To perform a reaction, the starting materials are passed over a silica-supported reagent using EOF, reacted for a specified time, collected in the product reservoir and analysed using a chromatographic technique. As Figure 5 illustrates, 5 mg of 3-(1-piperazino)propyl-functionalised silica gel **1** ($4.75\times10^{-3}$ mmol) was packed into a borosilicate glass capillary (500 μm×3 cm) and in order to prevent loss of the reagent, micro porous silica frits were placed at either end.[22] The capillary was then primed with MeCN to remove any air, ensuring the formation of a complete circuit, and the capillary attached to two glass reservoirs. The reagents were manipulated through the device via the application of a voltage to the platinum electrodes placed in the reagent reservoirs. As Figure 7 illustrates, a 1:1 mixture of benzaldehyde **4** and ethylcyanoacetate **5** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). Application of 333 and 0 V $cm^{-1}$ resulted in the mobilisation of the reaction mixture through the packed bed at a flow rate of 0.5 μl $min^{-1}$.

After 20 min, the reaction products were collected in reservoir B, diluted with MeCN and analysed by GC-MS, whereby 98.3% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2** was obtained with respect to residual benzaldehyde **4** (Fig. 8). Consequently, in order to demonstrate the use of the aforementioned device for the continuous synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2**, the reactor was run continually over a period of 4.75 h (14 runs), whereby 0.025 g (0.124 mmol, 98.9%) of product **2** was prepared. As Table 1 illustrates, reproducible conversions of greater than 98% were obtained demonstrating device stability and reagent longevity. After analysis by GC-MS, the reaction products were collected and concentrated in vacuo, the crude product was then analysed by NMR. As Figure 9 illustrates, NMR confirms the successful

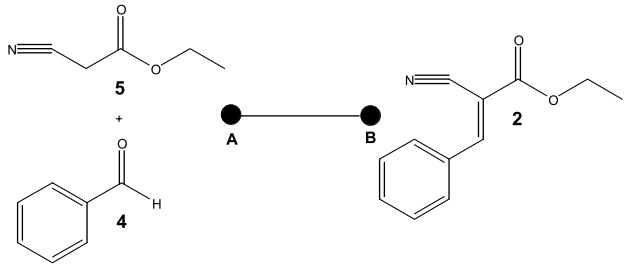



**Figure 7.** Schematic of the preparation of 2-cyano-3-phenyl acrylic acid ethyl ester **2** in an EOF-based miniaturised device.

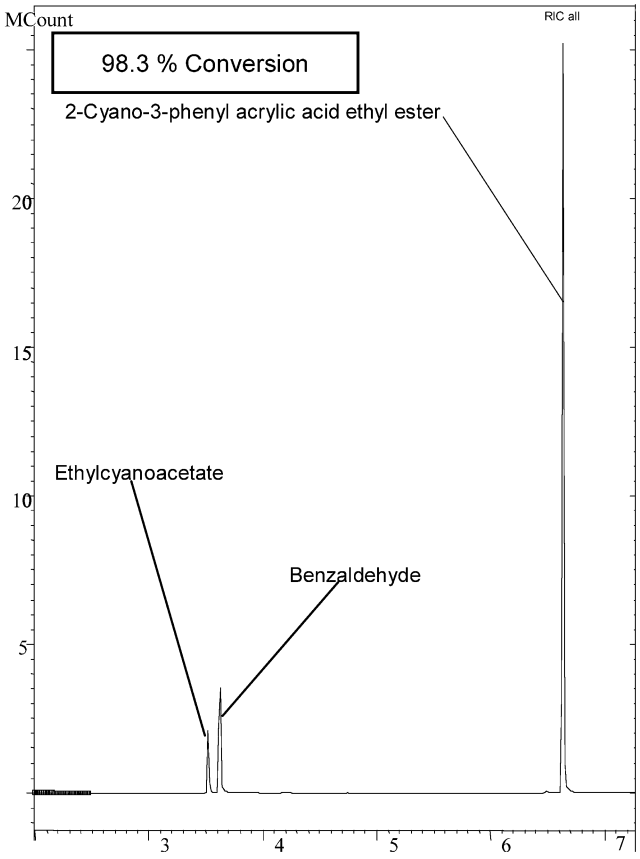



**Figure 8.** Chromatogram illustrating the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** within a micro reactor (98.3% conversion).

**Table 1.** Table illustrating device reproducibility over 4.7 h

| Run No. | Conversion (%) |
|---|---|
| 1 | 98.3 |
| 2 | 98.5 |
| 3 | 98.3 |
| 4 | 98.3 |
| 5 | 98.4 |
| 6 | 99.2 |
| 7 | 99.1 |
| 8 | 99.1 |
| 9 | 100.0 |
| 10 | 99.6 |
| 11 | 99.3 |
| 12 | 100.0 |
| 13 | 100.0 |
| 14 | 99.2 |
| Mean=99.1%, % RSD=0.65 | |

synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** in high purity within a micro fabricated device without the need for further purification. Having demonstrated the ability to synthesise 2-cyano-3-phenyl acrylic acid ethyl ester **2**, the technique was repeated using 4-bromobenzaldehyde **6**, 3,5-dimethoxybenzaldehyde **7**, 4-benzyloxybenzaldehyde **8**, to afford the respective condensation products **9**, **10** and **11** in 99.5, 94.7 and 95.1% conversion respectively (Table 2).

Having successfully demonstrated the preparation of an array of condensation products, the technique was extended to the synthesis of 2-benzylidene malononitrile **12**. Using the aforementioned methodology, a 1:1 mixture of malononitrile **13** and benzaldehyde **4** (40 μl, 1.0 M) in MeCN was placed in reservoir A and MeCN in reservoir B (40 μl). As malononitrile **13** exhibits a greater electroosmotic mobility cf. ethylcyanoacetate **5**, the applied field was

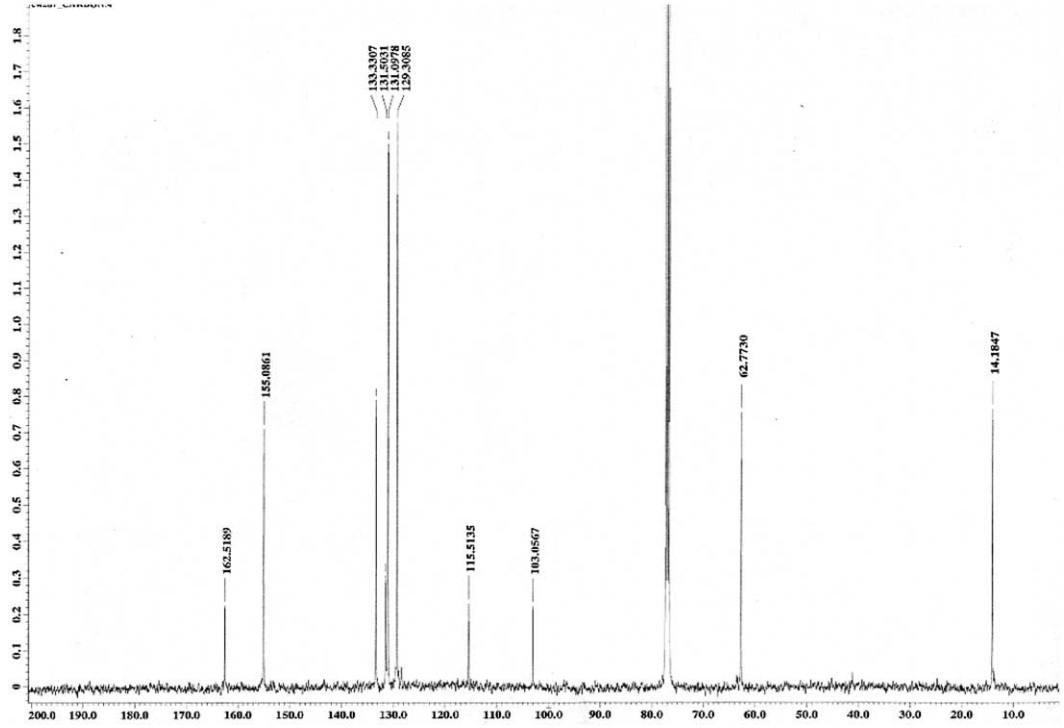



**Figure 9.** $^{13}$C NMR of 2-cyano-3-phenyl acrylic acid ethyl ester **2** synthesised using a micro fabricated device.

**Table 2.** Summary of the conversions obtained in a micro fabricated device using 3-(1-piperazino)propyl-functionalised silica gel **1**

| Product No. | Applied Field ($V\ cm^{-1}$) | Flow Rate ($\mu l\ min^{-1}$) | Conversion[a] (%) |
|---|---|---|---|
| **2** | 333 | 0.5 | 99.1 |
| **9** | 333 | 0.3 | 99.5 |
| **10** | 333 | 0.3 | 94.7 |
| **11** | 333 | 0.5 | 95.1 |
| **12** | 167 | 1.0 | 96.9 |
| **14** | 167 | 0.5 | 96.3 |
| **15** | 167 | 0.7 | 97.8 |
| **16** | 167 | 1.0 | 99.7 |

[a] $\geq$10 replicates were performed for each compound.

reduced in order to obtain comparable flow rates. Application of 167 and 0 V $cm^{-1}$ resulted in the mobilisation of the reaction mixture through the packed bed, at a flow rate of 1.0 µl $min^{-1}$, resulting in 96.9% conversion to 2-benzylidene malononitrile **12**. This was subsequently repeated using 4-bromobenzaldehyde **6**, 3,5-dimethoxybenzaldehyde **7**, 4-benzyloxybenzaldehyde **8**, to afford 2-(4-bromobenzylidene)-malononitrile **14** (96.9%), 2-(3,5-dimethoxybenzylidene)-malononitrile **15** (96.3%) and 2-(4-benzyloxybenzylidene)-malononitrile **16** (97.3%) respectively (Table 2). Again, $^{1}H$ and $^{13}C$ NMR spectra were obtained for all compounds synthesised within the device demonstrating excellent product purity. In all cases, no by-product formation was observed by GC-MS or NMR spectroscopy. The technique was subsequently repeated using the reagents; 3-(dimethylamino)propyl-functionalised silica gel **17** (1.50 mmol N $g^{-1}$), 3-aminopropyl-functionalised silica gel **18** (1.00 mmol N $g^{-1}$) and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]-pyrimidino)-propyl-functionalised silica gel **19** (2.4 mmol N $g^{-1}$) (Fig. 10) whereby 99.4, 100 and 99.3% conversion to 2-cyano-3-phenyl acrylic acid ethyl ester **2** were obtained.

Previous work by Macquarrie et al.,[23] demonstrated the use of a 3-aminopropyl-functionalised silica surface in a heated, pressure-driven, aluminium micro reactor. Operating the device at 98 °C enabled 70% conversion of a 1:1 ethylcyanoacetate **5** and benzaldehyde **4** to 2-cyano-3-phenyl acrylic acid ethyl ester **2**. Compared to the work described herein, this approach is disadvantageous as solvent-free techniques are only suitable for the preparation of low viscosity compounds. Also, the elevated reaction temperatures employed, compromises device simplicity. This investigation therefore focussed on the preparation of an array of condensation products at room temperature, within an EOF-based micro fabricated device (Table 3).

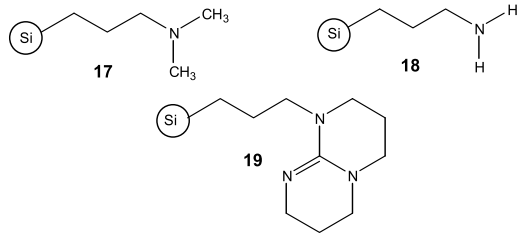



**Figure 10.** Schematic of 3-(dimethylamino)propyl-functionalised silica gel **17**, 3-aminopropyl-functionalised silica gel **18** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidino)propyl-functionalised silica gel **19**.

**Table 3.** Comparison of the conversions obtained for the synthesis of 2-cyano-3-phenyl acrylic acid ethyl ester **2** using silica-supported bases **1**, **17**, **18** and **19**

| Base | Applied field ($V\ cm^{-1}$) | Flow rate ($\mu l\ min^{-1}$) | Conversion[a] (%) |
|---|---|---|---|
| **1** | 333 | 0.5 | 99.1 |
| **17** | 333 | 0.35 | 99.4 |
| **18** | 333 | .35 | 100.0 |
| **19** | 333 | 0.80 | 99.3 |

[a] $\geq$10 replicates were performed for each compound.

Using four silica-supported bases, 3-(1-piperazino)propyl-functionalised silica gel **1**, 3-(dimethylamino)propyl-functionalised silica gel **17**, 3-aminopropyl-functionalised silica gel **18** and 3-(1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidino)propyl-functionalised silica gel **19**, enabled the synthesis of an array of condensation products in excellent conversions when the device was operated at flow rates of $<$1.0 µl $min^{-1}$. This technique is therefore suitable for the rapid synthesis of small quantities of compound for biological screening or the preparation of larger quantities by scaling-out.[24] The ability to prepare pure compounds in sufficient quantities to obtain structural information is also advantageous as it negates the need to prepare synthetic standards, whilst demonstrating the preparation of compounds of analytical purity. Compared to standard batch techniques employing solid supported reagents, the use of a continuous flow reactor is advantageous as reagents can be recycled without any loss upon filtration, resulting in more consistent conversions over extended periods of operation (Table 1 cf. Fig. 3). Localised concentration gradients enable reactions to be driven to completion without the need to employ large quantities of reagent, that is, 5 mg ($4.75\times10^{-4}$ mmol) in a micro reactor enables conversions in excess of 95% to be attained in minutes compared with $>$95 h in batch (Fig. 4, 0.0125 mmol).

## 3. Conclusions

In conclusion, we have demonstrated the successful incorporation of a series of silica-supported bases within an EOF-based micro-fabricated device, enabling the synthesis and characterisation of eight condensation products. Using the methodology described herein, further studies are currently underway within our laboratories to extend both the type of reagent and support employed, enabling more complex syntheses to be demonstrated.

## 4. Experimental

### 4.1. Materials and methods

All materials (analytical grade) were purchased from Aldrich and were used without purification. All NMR spectra were recorded as solutions in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. The spectra were recorded on a Joel GX400 spectrometer and the chemical shifts are given in parts per million (ppm) with coupling constants given in Hertz (Hz). The following abbreviations are used to report NMR data; s=singlet, d=doublet, t=triplet, br s=broad singlet, m=

multiplet and $C_0$=quaternary carbon. Gas chromatography-mass spectrometry (GC-MS) was performed using a Varian GC (CP-3800) coupled to a Varian MS (2000) with a CP-Sil 8 (30 m) column (Phenomenex) and ultra high purity helium (99.999% Energas) carrier gas. Samples were analysed using one of the following methods; Method A: injector temperature 250 °C, helium flow rate 1.0 ml $min^{-1}$, oven temperature 60 °C for 1.0 min and then ramped to 270 °C at 35 °C $min^{-1}$, with a 3.0 min filament delay or; Method B: injector temperature 250 °C, helium flow rate 1.0 ml $min^{-1}$, oven temperature 60 °C for 1.0 min and then ramped to 270 °C at 20 °C $min^{-1}$, with a 3.0 min filament delay.

### 4.2. Batch reactions

**4.2.1. General procedure for the solution-phase synthesis of Knoevenagel condensation products in batch.** Piperazine **3** (0.09 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml $mmol^{-1}$). After stirring overnight, the reaction mixture was concentrated in vacuo prior to the addition of dilute HCl (50 ml, 0.1 M) and the reaction products extracted into DCM (3×50 ml). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, subsequent recrystallisation from DCM/hexane afforded the respective condensation product.

**4.2.2. General procedure for the solid-phase synthesis of Knoevenagel condensation products in batch.** 3-(1-Piperazino)propyl-functionalised silica gel **1** (1.9 mmol N $g^{-1}$, 200–400 mesh) (0.10 g, 0.1 mmol) was added to a stirred solution of activated methylene (1.0 mmol) and aldehyde (1.0 mmol) in anhydrous MeCN (10 ml $mmol^{-1}$). After stirring overnight, the reaction mixture was filtered and the filtrate concentrated in vacuo to afford the respective condensation product.

### 4.3. Micro-scale methodology

The reactions described herein were carried out using a single capillary device, as illustrated in Figure 5, with capillary dimensions of 500 μm i.d.×3.0 cm. To hold the supported reagent in place, micro porous silica frits were placed at either end of the capillary.[22] To mobilise reagents by EOF, platinum electrodes (0.5 mm o.d.×2.5 cm) were placed within the reagent reservoirs and voltages applied using a Paragon 3B high-voltage power supply (HVPS), capable of applying 0–1000 V to four pairs of outputs (Kingfield Electronics). Automation of the HVPS was achieved using an in-house LabVIEW™ program. To enable the results obtained to be attained using devices of different dimensions, voltages are reported as applied fields (V $cm^{-1}$), that is, voltage/capillary length. To monitor the progress of the reaction, experiments were conducted over a period of 20 min, after which, the product reservoir was analysed by GC-MS, whereby comparison of the amount of product with respect to residual aldehyde enabled the percentage conversion to be determined. In order to obtain NMR data on the compounds synthesised in the flow system, the reactors were operated continuously for 3–5 h, after which the reaction products were concentrated in vacuo and the crude compound analysed.

**4.3.1. 2-Cyano-3-phenyl acrylic acid ester 2[25].** (0.0253 g, 98.9%) as a white solid; $\delta_H$ 1.41 (3H, t, $J$=7.0 Hz, $CH_2CH_3$), 4.39 (2H, q, $J$=7.0 Hz, $CH_2CH_3$), 7.53 (3H, m, Ar), 7.99 (2H, m, Ar) and 8.26 (1H, s, CH); $\delta_C$ 14.2 ($CH_3$), 62.8 ($CH_2$), 103.1 ($C_0CN$), 115.5 (CN), 129.3 (2×CH), 131.0 (2×CH), 131.5 ($C_0$), 133.3 (CH), 155.1 (CH) and 162.5 (CO); *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 (Method A) $R_T$=6.63 min.

**4.3.2. 3-(4-Bromophenyl)-2-cyano acrylic acid ethyl ester 9[26].** (0.0118 g, 99.5%) as a white solid; $\delta_H$ 1.40 (3H, t, $J$=7.3 Hz, $CH_2CH_3$), 4.39 (2H, q, $J$=7.3 Hz, $CH_2CH_3$), 7.65 (2H, d, $J$=8.7 Hz, Ar), 7.86 (2H, d, $J$=8.7 Hz, Ar) and 8.19 (1H, s, CH); $\delta_C$ 14.2 ($CH_3$), 62.9 ($CH_2$), 103.7 ($C_0CN$), 115.3 (CN), 128.3 ($C_0Br$), 130.3 ($C_0$), 132.3 (2×CH), 132.7 (2×CH), 153.6 (CH) and 162.3 (CO); 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 (Method B) $R_T$=10.84 min.

**4.3.3. 3-(3,5-Dimethoxyphenyl)-2-cyano acrylic acid ethyl ester 10[27].** (0.0109 g, 99.5%) as a white solid; $\delta_H$ 1.40 (3H, t, $J$=7.0 Hz, $CH_2CH_3$), 3.85 (6H, s, 2×$OCH_3$), 4.39 (2H, q, $J$=7.0 Hz, $CH_2CH_3$), 6.65 (1H, m, Ar), 7.15 (2H, m, Ar) and 8.17 (1H, s, CH); $\delta_C$ 14.2 ($CH_3$), 55.7 (2×$OCH_3$), 62.8 ($CH_2$), 103.4 ($C_0CN$), 106.2 (CH), 108.6 (2×CH), 115.6 (CN), 133.1 ($C_0$), 155.2 (CH), 161.1 (2×$C_0$) and 162.5 (CO); 262 ($M^+$+1, 20%), 261 (100), 189 (55), 161 (25) and 77 (10); GC-MS retention time (Method A) $R_T$=8.06 min.

**4.3.4. 3-(4-Benzyloxyphenyl)-2-cyano acrylic acid ethyl ester 11.** (0.0211 g, 99.1%) as a cream solid (Found C, 74.51; H, 5.77; N, 4.62. $C_{19}H_{17}O_3N$ requires C, 74.25; H, 5.58; N, 4.56%); $\delta_H$ 1.39 (3H, t, $J$=7.3 Hz, $CH_2CH_3$), 4.37 (2H, q, $J$=7.3 Hz, $CH_2CH_3$), 5.15, (2H, s, $CH_2$), 7.00 (2H, d, $J$=8.7 Hz, Ar), 7.40 (5H, m, Ar), 7.99 (2H, d, $J$=8.7 Hz, Ar) and 8.17 (1H, s, CH); $\delta_C$ 14.2 ($CH_3$), 62.5 ($CH_2$), 70.4 ($C_0CH_2$), 99.5 ($C_0$), 115.6 (2×CH), 124.6 (CN), 127.5 (2×CH), 128.4 (CH), 128.8 (2×CH), 133.7 (2×CH), 135.8 ($C_0$), 154.4, (CH), 162.9 ($OC_0$) and 163.1 (CO); 308 ($M^+$+1, 5%), 307 (20), 91 (100) and 65 (20); GC-MS retention time (Method B) $R_T$=12.35 min.

**4.3.5. 2-Benzylidene-malononitrile 12[25].** (0.0154 g, 100%) as a pale yellow solid; $\delta_H$ 7.55 (2H, m, Ar), 7.64 (1H, m, Ar), 7.79 (1H, s, CH) and 7.91 (2H, m, Ar); $\delta_C$ 83.0 ($C_0$), 112.6 (CN), 113.7 (CN), 129.7 (2×CH), 130.8 (2×CH), 131.0 ($C_0$), 134.7 (CH) and 159.9 (CH); 155 ($M^+$+1, 20%), 154 (100), 127 (20) and 76 (10); GC-MS retention time (Method A) $R_T$=5.84 min.

**4.3.6. 2-(4-Bromobenzylidene)-malononitrile 14[28].** (0.0349 g, 99.9%) as a pale yellow solid; $\delta_H$ 7.69 (2H, d, $J$=8.4 Hz, Ar), 7.72 (1H, s, CH) and 7.77 (2H, d, $J$=8.4 Hz, Ar); $\delta_C$ 83.6 ($C_0$), 112.3 (CN), 113.5 (CN), 129.7 ($C_0Br$), 130.0 ($C_0$), 131.8 (2×CH), 133.1 (2×CH) and 158.4 (CH); 235 ($M^+$+1, 70%), 234 (100), 233 (95), 232 (90), 153 (25) and 77 (10); GC-MS retention time (Method B) $R_T$=9.65 min.

**4.3.7. 2-(3,5-Dimethoxybenzylidene)-malononitrile 15[25].**

(0.0240 g, 99.2%) as a yellow solid; $\delta_H$ 3.84 (6H, s, $OCH_3$), 6.70 (1H, m, Ar), 7.03 (2H, m, Ar) and 7.69 (1H, s, CH); $\delta_C$ 55.7 (2×$OCH_3$), 83.2 ($C_0$), 107.3 (CH), 108.3 (2×CH), 112.7 (CN), 113.7 (CN), 132.4 ($C_0$), 160.1 (CH) and 161.3 (2×$C_0OCH_3$); 215 ($M^+ + 1$, 25%), 214 (100), 186 (55), 171 (20), 155 (20), 142 (15), 114 (10) and 76 (10); GC-MS retention time (Method A) $R_T = 7.50$ min.

**4.3.8. 2-(4-Benzyloxybenzylidene)-malononitrile 16[29].** (0.0235 g, 99.6%) as a pale yellow solid; $\delta_H$ 5.17 (2H, s, $CH_2$), 7.08 (2H, d, $J = 9.0$ Hz, Ar), 7.39 (5H, m, Ar), 7.64 (1H, s, CH) and 7.90 (2H, d, $J = 9.0$ Hz, CH); $\delta_C$ 70.6 ($CH_2$), 78.8 ($C_0$), 113.3 (CN), 114.4 (CN), 116.0 (2×CH), 124.2 ($C_0$), 127.5 (2×CH), 128.6 (CH), 128.9 (2×CH), 133.5 (2×CH), 135.5 ($C_0$), 158.8 (CH) and 163.9 ($OC_0$); 261 ($M^+ + 1$, 5%), 260 (5), 114 (10) and 91 (100); GC-MS retention time (Method B) $R_T = 11.97$ min.

## Acknowledgements

Full financial support provided by the EPSRC (Grant No. GR/S34106/01) is gratefully acknowledged. Mike Bailey (University of Hull) is also acknowledged for assistance in the device fabrication.

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