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Solution phase synthesis of esters within a micro reactor

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Abstract—A range of techniques are demonstrated for the solution phase synthesis of esters within an EOF-based borosilicate glass micro reactor, including the use of mixed anhydrides and the in situ preparation of acyl halides.

1. Introduction

Over the past five years, interest in the miniaturisation of chemical synthesis has grown rapidly with the desire to miniaturise being driven by the need for greater process control.[1] Due to the predictable thermal and mass transportation properties observed within a micro reactor a high degree of reaction control is obtained.[2] Also, the inherently high surface to volume ratio obtained is advantageous, enabling heat generated by exothermic reactions to be dissipated rapidly, reducing the likelihood of thermal runaway. Using an approach referred to as scale-out or numbering-up,[3] a reaction is firstly optimised within the laboratory using a single micro reactor and in order to increase production volume, the number of reactors employed is simply increased. Consequently, a reaction is only optimised once and all subsequent reactors are controlled using the same operating conditions, making the technique cost effective, time saving and flexible. With these factors in mind, micro reaction technology is of particular interest to the pharmaceutical industry, where long term objectives include the desire to perform multiple functions such as synthesis, screening, detection and biological evaluation on a single integrated device, resulting in an overall reduction in the time taken to discover new lead compounds and put them into production.[4]

In the context of this paper, a micro reactor is defined as a device containing a series of interconnecting channels formed in a planar substrate, with dimensions in the range of 10–400 μm.[5] Depending on the application of the device, a range of substrates have been employed,[6] however due to its compatibility with organic solvents, high mechanical strength, temperature resistance and optical transparency, borosilicate glass is the chosen substrate for the work described herein. The device consists of a borosilicate glass base plate, containing an etched channel network; and a top block, containing 3 mm drilled holes to form the reagent reservoirs.[7] Thermal bonding of the two layers affords a sealed micro reactor, with typical dimensions in the range of 2.5 cm×2.5 cm×2.0 cm (Fig. 1). In order to perform a reaction, reagents are brought together within the micro channel using a suitable pumping mechanism, in this case electroosmotic flow (EOF),[8] reacted for a specified period of time and the reaction products collected in the product reservoir and analysed using a suitable chromatographic technique. Using this approach, a number of groups have successfully synthesised a range of compounds, including; azo dyes,[9] stilbene esters,[10,11] peptides,[12] 1,3-diketones[13] and α,β-unsaturated carbonyl compounds,[14] demonstrating reduced reaction times, enhanced conversions and reaction stereoselectivity.

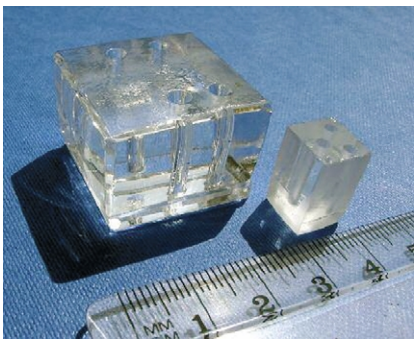

Figure 1. A typical borosilicate glass micro reactor.

For many years, functional group incompatibility remained a problem for synthetic chemists, until Emil Fischer[15] developed the notion that an otherwise reactive group could be temporarily rendered inert by the use of a 'protecting group'. In complex systems, such as the synthesis of peptides,[12] there is often a need for more than one protecting group, it is therefore crucial that the groups can be added

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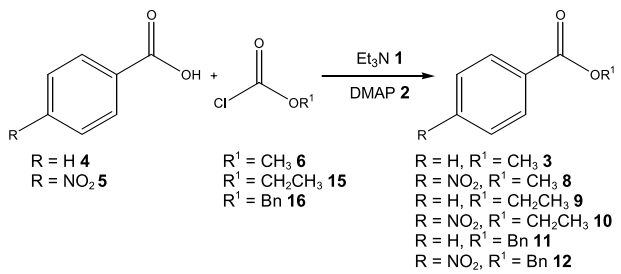
and removed selectively. The widespread use of carboxyl groups in organic synthesis has lead to a great deal of work in the field of carboxyl protection.[16] Although many techniques are available within the literature for the transformation of carboxylic acids to esters, there remains a need for mild and rapid techniques that enable the efficient protection of the carboxyl group in base sensitive molecules.[17] Many of the existing techniques however are not suitable for use within an electrokinetic environment due to the extremes of pH (acid/base catalysed) and elevated reaction temperatures employed. Consequently, the catalytic conversion of mixed anhydrides to esters, demonstrated by Kim et al.[18] was of considerable interest, as the reaction was found to proceed rapidly and in high yield, whilst employing mild reaction conditions.

2. Results and discussion

2.1. Use of alkyl chloroformates within a micro reactor

In order to investigate the use of alkyl chloroformates within a micro reactor and highlight any advantages associated with the use of this technique, a series of synthetic standards were prepared and characterised in batch (Scheme 1). The alkyl chloroformate was added to a stirred solution of carboxylic acid and triethylamine **1** at 0°C, after stirring for 5 min DMAP **2** was added (0.5 equiv.) to afford the respective ester. Although the reaction is traditionally performed in DCM, this solvent exhibits no electroosmotic mobility therefore alternative solvent systems were investigated. As solvents such as DMF are incompatible with alkyl chloroformates, prior to transferring the reaction from batch to a micro reactor, the reaction was investigated using anhydrous MeCN. As Table 1 illustrates, comparable conversions were obtained for the preparation of benzoic acid methyl ester **3** in both DCM and MeCN, consequently all synthetic standards were prepared using anhydrous MeCN as solvent.



Scheme 1. Preparation of an array of esters using alkyl chloroformates.

Table 1. Comparison of conversions obtained for the preparation of benzoic acid methyl ester **3** using anhydrous MeCN and DCM

Solvent	Conversion (%)	
	30 min	24 h
DCM	44	67
MeCN	46	69

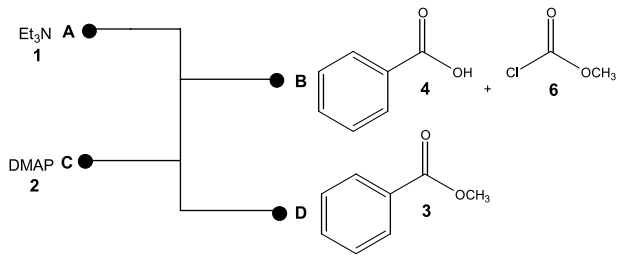
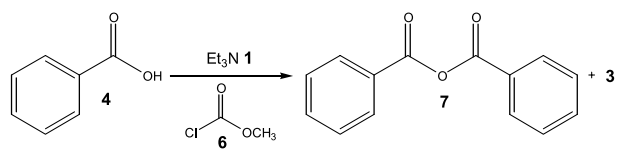


Figure 2. Schematic of the reactor manifold used to synthesise benzoic acid methyl ester **3**.

Using the reaction manifold illustrated in Figure 2, the preparation of benzoic acid methyl ester **3** was investigated within a micro reactor; a standard solution of triethylamine **1** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir A, a solution of benzoic acid **4** and methyl chloroformate **6** (40 μl, 1.0 M) in anhydrous MeCN in reservoir B, a solution of DMAP **2** (40 μl, 0.5 M) in anhydrous MeCN in reservoir C and the reaction products collected in anhydrous MeCN in reservoir D over a period of 20 min. The reagents were manipulated within the device using the following applied fields, 276, 400, 318 and 0 V cm^{-1} (A, B, C and D respectively). Analysis of the reaction products by GC–MS illustrated 100% conversion of benzoic acid **4** to the ester **3**.

The reaction was subsequently repeated without DMAP **2** in order to investigate whether or not the ester **3** could be prepared in the absence of a catalyst; a standard solution of triethylamine **1** (40 μl, 1.0 M) in anhydrous MeCN was added to reservoir A, a solution of benzoic acid **4** (40 μl, 1.0 M) in anhydrous MeCN in reservoir B, a solution of methyl chloroformate **6** (40 μl, 1.0 M) in reservoir C and the reaction products were collected in anhydrous MeCN at reservoir D. The reagents were manipulated using the following applied fields, 276, 400, 400 and 0 V cm^{-1}. Although subsequent analysis of the reaction products by GC–MS illustrated ester **3** formation (ca. 20% conversion), the reaction mixture also contained a significant quantity of benzoic anhydride **7** (Scheme 2), a phenomenon previously reported by Kim et al.[19] As a result of this observation, all subsequent micro reactions were performed using 0.5 equiv. of DMAP **2**.



Scheme 2. Preparation of the by-product benzoic anhydride **7**.

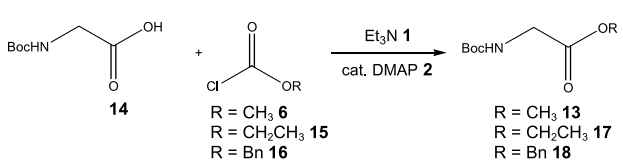
In order to further demonstrate the technique, the preparation of 4-nitrobenzoic acid methyl ester **8** was investigated. A standard solution of triethylamine **1** (40 μl, 0.5 M) in anhydrous MeCN was placed in reservoir A, a solution of 4-nitrobenzoic acid **5** and methyl chloroformate **6** (40 μl, 0.5 M) in anhydrous MeCN in reservoir B, a solution of DMAP **2** (40 μl, 0.25 M) in anhydrous MeCN in reservoir C and the reaction products collected in anhydrous MeCN in reservoir D. The reagents were manipulated within the device using the following applied fields, 345, 400, 455 and 0 V cm^{-1}, to afford 100% conversion of 4-nitrobenzoic acid

Table 2. Comparison of the conversions obtained for the preparation of esters **3**–**12** in a micro reactor with those in batch

Product No.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
3	67	100	276, 400, 318, 0
8	95	100	345, 400, 455, 0
9	100	95	345, 400, 455, 0
10	93	98	385, 396, 386, 0
11	80	91	345, 200, 455, 0
12	98	100	345, 400, 455, 0

5 to the methyl ester **8**. Using the aforementioned methodology, the technique was extended to the preparation of ethyl esters **9** and **10**, and benzyl esters **11** and **12**. In all cases, compared to the esterification of benzoic acid **4**, reduced reagent concentrations were employed for all 4-nitrobenzoic acid **5** micro reactions due lower reagent solubility in anhydrous MeCN. As Table 2 illustrates, in all cases, comparable conversions were obtained within a micro reactor compared to the batch technique.

As previously mentioned, the protection of the carboxyl group is an important transformation used in the synthesis of peptides, the technique was therefore extended to the preparation of a series of Boc-glycine esters (Scheme 3). Using the following procedure, Boc-glycine methyl ester **13** was subsequently prepared within a micro reactor; a standard solution of triethylamine **1** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir A, a solution of Boc-glycine **14** and methyl chloroformate **6** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir B, a solution of DMAP **2** (40 μl, 0.5 M) in anhydrous MeCN in reservoir C and the reaction products collected at reservoir D in anhydrous MeCN. The reagents were manipulated within the device using the following applied fields, 385, 417, 364 and 0 V cm^{-1}, resulting in 100% conversion of Boc-glycine **14** to Boc-glycine methyl ester **13**. The technique was further exemplified using ethyl chloroformate **15** and benzyl chloroformate **16** to afford the respective ethyl ester **17** and benzyl ester **18** in quantitative conversion. As Tables 2 and 3 illustrate, we have successfully transferred a simple room temperature technique for the preparation of esters from batch to a micro reactor, demonstrating enhanced or equivalent conversions compared to those obtained in batch. In all cases when employing DMAP **2**, no undesirable anhydride formation was observed.



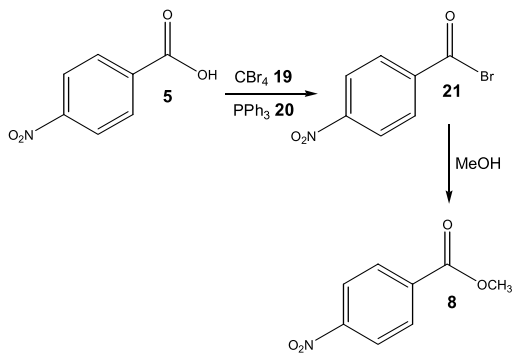
Scheme 3. Preparation of Boc-glycine esters **13**, **17** and **18**.

Table 3. Conversions obtained for the preparation of Boc-glycine esters

Product No.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
13	100	100	385, 417, 364 and 0
17	100	100	385, 417, 364 and 0
18	100	100	385, 417, 364 and 0

2.2. In situ preparation of an acyl bromide

Having successfully demonstrated the synthesis of esters via the mixed anhydride approach, the investigation was extended to incorporate the preparation of esters via and acyl halide. As Scheme 4 illustrates, treatment of 4-nitrobenzoic acid **5** with CBr_4 **19**/PPh_3 **20** (1:2),[19–21] enabled the preparation of the acyl halide 4-nitrobenzoyl bromide **21**. Subsequent quenching of the acyl bromide **21** with anhydrous MeOH afforded the methyl ester **8** in 100% conversion over the two-step synthesis.



Scheme 4. Preparation of an acyl bromide using CBr_4 **26**/PPh_3 **27**.

Using the manifold illustrated in Figure 3, the in situ preparation of an acyl halide and subsequent ester formation was investigated. A standard solution of 4-nitrobenzoic acid **5** (40 μl, 0.2 M) in anhydrous MeCN was placed in reservoir A, a solution of CBr_4 **19** (40 μl, 0.2 M) in anhydrous MeCN in reservoir B and a solution of PPh_3 **22** (40 μl, 0.4 M) in anhydrous MeCN in reservoir C. In order to detect the formation of 4-nitrobenzoyl bromide **21** as the methyl ester **8**, the reaction products were collected in anhydrous MeOH at reservoir D. Manipulation of the reagents within the device using the following applied fields, 385, 417, 455 and 0 V cm^{-1}, resulted in a disappointing 11% conversion to the methyl ester **8** with respect to residual 4-nitrobenzoic acid **5**. The low conversion obtained compared to batch is attributed to the poor electroosmotic flow exhibited by the PPh_3 **20**, therefore in order to improve reagent flow, the concentration of PPh_3 **20** was reduced. Using 0.2 M standard solutions, the reagents were mobilised using the applied fields, 385, 417, 455 and 0 V cm^{-1}, whereby 6% conversion to the ester **8** was obtained.

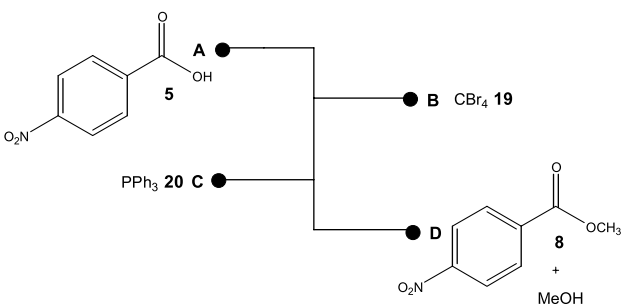
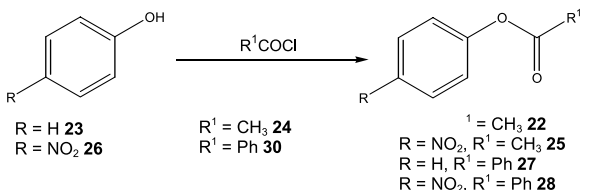


Figure 3. Schematic of the manifold used for the synthesis of ester **8**.

Although initial studies illustrate poor conversion within the micro reactor (11%), attributed to poor mobilisation of the PPh_3 **20**, further investigations into solvent system, concentration of reagents and pumping mechanism are required in order to fully evaluate the feasibility of this approach within a micro reactor. Alternatively, polymer-supported PPh_3 could be used with the added advantage being that resulting products are free from triphenylphosphine oxide. Through investigating the above parameters, the in situ generation and subsequent reaction of acyl halides should prove to be a synthetically useful transformation within a micro reactor.

2.3. Preparation of phenolic esters within a micro reactor

Phenyl acetate **22** formed via the acetylation of phenol **23**, Scheme 5 is a synthetically useful compound as subsequent Fries rearrangement leads to the pharmaceutically important hydroxyacetophenone.[22] Having successfully demonstrated the preparation of esters using the mixed anhydride technique, the investigation was extended to the preparation of phenolic esters. Due to the acidity of the phenolic proton, the preparation of phenolic esters can be performed using relatively mild conditions, therefore having previously demonstrated the mobilisation of triethylamine **1** by EOF, the organic base was again investigated.



Scheme 5. Preparation of a series of phenolic esters.

Using the following procedure, the preparation of acetic acid phenyl ester **22** was investigated; a standard solution of triethylamine **1** (40 μl, 2.0 M) in anhydrous MeCN was placed in reservoir A, a standard solution of phenol **23** (40 μl, 2.0 M) in anhydrous MeCN was placed in reservoir B, a solution of acetyl chloride **24** (40 μl, 2.0 M) in anhydrous MeCN in reservoir C (Fig. 4). The reagents were manipulated within the device using the following applied fields, 345, 400, 364 and 0 V cm^{-1} and the reaction products collected in anhydrous MeCN at reservoir D. Analysis of the reaction products by GC–MS illustrated 100% conversion of phenol **23** to the ester **22** had occurred.

Having successfully demonstrated the preparation of acetic acid phenyl ester **22**, the preparation of acetic acid 4-nitrophenyl ester **25** was investigated. Again, a standard

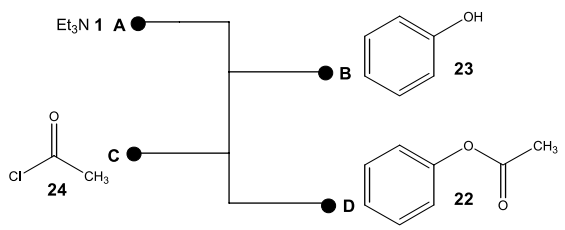


Figure 4. Schematic of the reaction manifold used for the preparation of acetic acid phenyl ester **22**.

Table 4. Conversions obtained for the preparation of phenolic esters

Product No.	Conversion (%)		Applied field (V cm^{-1})
	Batch	Micro reaction	
22	93	100	345, 400, 364, 0
25	73	77	345, 375, 455, 0
27	96	100	308, 333, 364, 0
28	74	87	259, 308, 364, 0

solution of triethylamine **1** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir A, a solution of 4-nitrophenol **26** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir B, a solution of acetyl chloride **24** (40 μl, 1.0 M) in anhydrous MeCN was placed in reservoir C and the reaction products collected in anhydrous MeCN at reservoir D. The reagents were manipulated within the device using the following applied fields, 345, 375, 455 and 0 V cm^{-1}, whereby 77% conversion to the ester **25** was observed (with respect to residual 4-nitrophenol **26**). As the preparation of acetic acid phenyl esters proved successful, the study was extended to the preparation of benzoic acid phenyl esters **27** and **28** whereby 100% and 87% conversion were obtained respectively. As Table 4 illustrates, in all cases, enhancements in conversion were obtained compared to batch.

3. Conclusions

Previous work by Wilson et al.[23] demonstrated catalytic esterification within a heated PDMS/glass micro reactor by incorporating a solid acid catalyst into the channel network. Operating the device at 180°C enabled 35% conversion of a 1:1 ethanol and ethanoic acid solution to ethyl acetate to be obtained using pressure-driven flow. Compared to the work described herein, this approach is disadvantageous, as elevated reaction temperatures are required to enable relatively moderate conversions to be obtained. This investigation therefore focussed on the preparation of an array of esters within a micro reactor at room temperature.

In conclusion we have demonstrated a range of techniques for the preparation of esters within an EOF-based, borosilicate glass micro reactor. With the exception of the in situ preparation of acyl bromides, excellent conversions were obtained for all examples investigated. Further studies are currently underway within our laboratories in order to improve the conversions obtained for the in situ preparation of an acyl halide via the use of diphenyldibromophosphorane and to utilise the chemistry in more complex natural product synthesis.

4. Experimental

4.1. Materials and methods

All solvents were purchased as anhydrous grade over molecular sieves from Fluka Chemie. Reagents (analytical grade) were purchased from Sigma-Aldrich and unless otherwise stated, were used without purification. Nuclear magnetic resonance (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 in Hertz (Hz). Elemental combustion analyses were performed using a Fisons Carlo Erba EA1108 analyser. Gas Chromatography–Mass Spectrometry data was obtained 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 the following method, injector temperature 200°C, helium flow rate 1 ml min^{-1}, oven temperature 50°C for 4 min then ramped to 250°C at 30°C min^{-1}, with a 3.0 min filament delay.

4.2. Micro reactor methodology

The reactions described herein were carried out using a 4 channel borosilicate glass micro reactor, as illustrated in Figure 2, with channel dimensions of 350 μm (wide) ×52 μm (deep) ×2.5 cm (long).[8,24] In order to minimise the effect of pressure gradients within the micro channels, micro porous silica frits were placed within the channels.[25] In order 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, Sheffield, UK). Automation of the HVPS using an in-house LabVIEW™ program enabled complex sequences of voltages to be investigated. To enable the results obtained to be applied to devices of different dimensions, voltages are reported as applied fields (V cm^{-1}) i.e. voltage/channel length. In order 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 starting material enabled the progression of the reaction to be determined.

4.3. Batch reactions

4.3.1. General procedure for the preparation of esters using alkyl chloroformates. A typical experimental procedure is as follows: Alkyl chloroformate in MeCN (0.5 ml per mmol) was added to a stirred solution of carboxylic acid (1 equiv.) and triethylamine **1** (1 equiv.) in MeCN (0.5 ml per mmol) under N_2 at 0°C. The reaction mixture was stirred for a further 5 min prior to the addition of DMAP **2** (0.5 equiv.) in MeCN (1 ml per mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the residue diluted with DCM (100 ml). The organic portion was washed with saturated sodium hydrogen carbonate (50 ml) followed by dilute hydrochloric acid (50 ml, 0.1 M). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford the ester. Residual DMAP **2** was subsequently triturated using DCM/hexane, to afford the respective ester.

4.3.2. Benzoic acid methyl ester 3.[26] Using methyl chloroformate **6** (0.16 ml, 2.05 mmol), benzoic acid **4** (0.25 g, 2.05 mmol) and DMAP **2** (0.13 g, 1.0 mmol), benzoic acid methyl ester **3** was obtained (0.19 g, 68%) as a colourless oil; spectroscopic data as previously reported in the literature.

4.3.3. 4-Nitrobenzoic acid methyl ester 8.[27] Using methyl chloroformate **6** (0.12 ml, 1.50 mmol), 4-nitrobenzoic acid **5** (0.25 g, 1.50 mmol) and DMAP **2** (0.09 g, 0.75 mmol), 4-nitrobenzoic acid methyl ester **8** was obtained (0.26 g, 97%) as a pale yellow solid; spectroscopic data as previously reported in the literature.

4.3.4. Benzoic acid ethyl ester 9.[27] Using ethyl chloroformate **15** (0.20 ml, 2.10 mmol), benzoic acid **4** (0.25 g, 2.10 mmol) and DMAP **2** (0.13 g, 1.05 mmol), benzoic acid ethyl ester **9** was obtained (0.29 g, 95%) as a pale yellow oil; spectroscopic data as previously reported in the literature.

4.3.5. 4-Nitrobenzoic acid ethyl ester 10.[27] Using ethyl chloroformate **15** (0.14 ml, 1.50 mmol), 4-nitrobenzoic acid **5** (0.25 g, 1.50 mmol) and DMAP **2** (0.09 g, 0.75 mmol), 4-nitrobenzoic acid ethyl ester **10** was obtained (0.27 g, 93%) as a yellow solid; spectroscopic data as previously reported in the literature.

4.3.6. Benzoic acid benzyl ester 11.[28] Using benzyl chloroformate **16** (0.29 ml, 2.05 mmol), benzoic acid **4** (0.25 g, 2.05 mmol) and DMAP **2** (0.12 g, 1.0 mmol), benzoic acid benzyl ester **11** was obtained (0.37 g, 85%) as a colourless oil; spectroscopic data as previously reported in the literature.

4.3.7. 4-Nitrobenzoic acid benzyl ester 12.[28] Using benzyl chloroformate **16** (0.21 ml, 1.50 mmol), 4-nitrobenzoic acid **5** (0.25 g, 1.50 mmol) and DMAP **2** (0.09 g, 0.75 mmol), 4-nitrobenzoic acid benzyl ester **12** was obtained (0.35 g, 90%) as a colourless oil; spectroscopic data as previously reported in the literature.

4.3.8. *tert*-Butoxycarbonylaminoacetic acid methyl ester 13.[28] Using methyl chloroformate **6** (0.11 ml, 1.42 mmol), Boc-glycine **14** (0.25 g, 1.42 mmol) and DMAP **2** (0.09 g, 0.71 mmol), the title compound **13** was obtained (0.26 g, 93%) as a colourless oil; spectroscopic data as previously reported in the literature.

4.3.9. *tert*-Butoxycarbonylaminoacetic acid ethyl ester 17. Using ethyl chloroformate **15** (0.14 ml, 1.42 mmol), Boc-glycine **14** (0.25 g, 1.42 mmol) and DMAP **2** (0.09 g, 0.71 mmol), the title compound **17** was obtained (0.27 g, 93%) as a colourless oil. (Found C, 52.93; H, 8.83; N, 7.03; $C_9H_{18}O_4N$ requires C, 52.90; H, 8.89; N, 6.86%); δ_H (400 MHz, $CDCl_3$/TMS) 1.28 (3H, t, J=7.0 Hz, CH_2CH_3), 1.45 (9H, s, 3×CH_3), 3.90 (2H, d, J=5.6 Hz, $NHCH_2CO$), 4.21 (2H, q, J=7.0 Hz, CH_2CH_3) and 5.11 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$/TMS) 14.1 (CH_2CH_3), 28.3 (3×CH_3), 42.4 ($C(CH_3)_3$), 61.3 (CH_2CH_3), 79.9 ($NHCH_2CO$), 155.7 (CO) and 170.4 (CCONH); m/z (E.I.) 204 (M^++1, 3%), 203 (5), 148 (100) and 104 (15); GC–MS R_T=5.69 min.

4.3.10. *tert*-Butoxycarbonylaminoacetic acid benzyl ester 18. Using benzyl chloroformate **16** (0.20 ml, 1.42 mmol), Boc-glycine **14** (0.25 g, 1.42 mmol) and DMAP **2** (0.09 g, 0.71 mmol), the title compound **18** was obtained (0.36 g,

96%) as a colourless oil. (Found C, 63.38; H, 7.42; N, 5.47 $C_{14}H_{20}O_4N$ requires C, 63.14; H, 7.57; N, 5.26%); δ_H (400 MHz, $CDCl_3$/TMS) 1.44 (9H, s, 3×CH_3), 3.95 (2H, d, J=5.6 Hz, $COCH_2NH$), 5.08 (1H, br s, NH), 5.17 (2H, s, CH_2Ph) and 7.36 (5H, m, Ar); δ_C (100 MHz, $CDCl_3$/TMS) 28.3 (3×CH_3), 42.5 ($C(CH_3)_3$), 67.0 (CH_2Ph), 80.0 ($NHCH_2CO$), 128.4 (2×CH), 128.5 (2×CH), 128.6 (CH), 135.2 (C_0), 155.7 (CO) and 170.3 (OCONH); *m/z* (E.I) 266 (M^++1, 1%), 265 (1), 256 (75), 166 (100) and 91 (25); GC–MS R_T=7.56 min.

4.3.11. Acetic acid phenyl ester 22.[29] Purified sodium hydride **29** (0.06 g, 2.33 mmol) in THF (5 ml) was added to a stirred solution of phenol **23** (0.20 g, 2.13 mmol) in THF (20 ml), after stirring at room temperature for 10 min, acetyl chloride **24** (0.17 g, 2.13 mmol) was added; the reaction mixture was stirred for a further 1 h prior to concentrating in vacuo. The aqueous layer was neutralised with sodium hydrogen carbonate (50 ml) and the product extracted into DCM (3×50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford, after recrystallisation (DCM/hexane), the ester **22** (0.26 g, 90%) as a cream solid; spectroscopic data as reported in the literature.

4.3.12. Acetic acid 4-nitrophenyl ester 25.[30] Purified sodium hydride **29** (0.10 g, 3.96 mmol) in THF (5 ml) was added to a stirred solution of 4-nitrophenol **26** (0.50 g, 3.59 mmol) in THF (20 ml), after stirring at room temperature for 10 min, acetyl chloride **24** (0.26 ml, 3.66 mmol) was added. The reaction mixture was stirred for a further 1 h and subsequently concentrated in vacuo, the aqueous layer was neutralised with sodium hydrogen carbonate (50 ml) and the product extracted into DCM (3×50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford, after recrystallisation (DCM/hexane), acetic acid-4-nitrophenyl ester **25** (0.43 g, 65.0%) as a colourless solid; spectroscopic data as previously reported in the literature.

4.3.13. Benzoic acid phenyl ester 27.[29] Purified sodium hydride **29** (0.06 g, 2.33 mmol) was added to a stirred solution of phenol **23** (0.20 g, 2.13 mmol) in THF (2 ml), after stirring at room temperature for 10 min, benzoyl chloride **30** (0.25 ml, 2.15 mmol) was added. The reaction mixture was stirred for 1 h and subsequently concentrated in vacuo, the aqueous layer was neutralised with sodium hydrogen carbonate (50 ml) and the product extracted into DCM (3×50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford, after recrystallisation (DCM/hexane), the ester **27** (0.41 g, 98%) as a pale yellow solid; spectroscopic data as previously reported in the literature.

4.3.14. Benzoic acid 4-nitrophenyl ester 28.[30] Purified sodium hydride **29** (0.10 g, 3.96 mmol) in THF (10 ml) was added to a stirred solution of 4-nitrophenol **26** (0.50 g, 3.59 mmol) in THF (25 ml). The reaction mixture was stirred for 10 min prior to quenching with benzoyl chloride **30** (0.50 g, 3.60 mmol). The reaction mixture was stirred for a further 1 h and subsequently concentrated in vacuo, the aqueous layer was neutralised with sodium hydrogen carbonate (50 ml) and the reaction products extracted into DCM (3×50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford, after recrystallisation (DCM/hexane), the ester **28** (0.85 g, 97%) as a cream solid; spectroscopic data as previously reported in the literature.

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References

1. Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293.
2. Schwalbe, T.; Volker, A.; Wille, G. *Chimia* **2002**, *56*, 636.
3. Ehrfeld, W.; Hessel, V.; Lowe, H. Microreactors: New Technology for Modern Chemistry; Wiley-VCH: New York, 2000.
4. Fletcher, P. D. I.; Haswell, S. J.; Pombo-Villar, E.; Warrington, B. H.; Watts, P.; Wong, S. Y. F.; Xhang, X. *Tetrahedron* **2002**, *58*, 4735.
5. Haswell, S. J.; Middleton, R. J.; O'Sullivan, B.; Skelton, V.; Watts, P.; Styring, P. *J. Chem. Soc., Chem. Commun.* **2001**, 391.
6. Duffy, D. C.; McDonald, J. C.; Schueller, O. J. A.; Whitesides, G. M. *Anal. Chem.* **1998**, *70*, 4974.
7. McCreedy, T. *Anal. Chim. Acta* **2001**, *427*, 39.
8. Fletcher, P. D. I.; Haswell, S. J.; Paunov, V. N. *Analyst* **1999**, *124*, 1273.
9. Salimi-Moosavi, H.; Tang, T.; Harrison, D. J. *J. Am. Chem. Soc.* **1997**, *68*, 2515.
10. Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B. H.; Wong, S. Y. F. *Analyst* **2001**, *126*, 7.
11. Skelton, V.; Greenway, G. M.; Haswell, S. J.; Styring, P.; Morgan, D. O.; Warrington, B. H.; Wong, S. Y. F. *Analyst* **2001**, *126*, 11.
12. Watts, P.; Wiles, C.; Haswell, S. J.; Pombo-Villar, E. *Tetrahedron* **2002**, *58*, 5427.
13. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *J. Chem. Soc., Chem. Commun.* **2002**, 1034.
14. Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Lab Chip* **2002**, *2*, 62.
15. Kocienski, P. J. Protecting Groups; Wiley: New York, 1994.
16. Haslam, E. *Tetrahedron* **1980**, *36*, 2409.
17. Pizey, J. S. *Synthetic Reagents*; Wiley: New York, 1974; Vol. 2. p 65.
18. Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365.
19. Posner, G. H.; Loomis, G. L.; Sawaya, H. S. *Tetrahedron Lett.* **1975**, *16*, 1373.
20. Rabinowitz, R.; Marcus, R. *J. Am. Chem. Soc.* **1962**, *84*, 1312.
21. Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Alberto Marco, J. *J. Chem. Soc., Chem. Commun.* **1985**, 296.
22. Olah, G. H.; Grant, J. L.; Westerman, P. W. *J. Org. Chem.* **1975**, *40*, 2103.
23. McCreedy, T.; Wilson, N. G. *Analyst* **2001**, *126*, 21.
24. Broadwell, I.; Fletcher, P. D. I.; Haswell, S. J.; McCreedy, T.; Zhang, X. *Lab Chip* **2001**, *1*, 66.

25. Christensen, P. D.; Johnson, S. W. P.; McCreedy, T.; Skelton, V.; Wilson, N. G. *Anal. Commun.* **1998**, *35*, 341.
26. Johnstone, R. A. W.; Price, P. J. *Tetrahedron* **1985**, *41*, 2493.
27. Hans, J. J.; Driver, R. W.; Burke, S. D. *J. Org. Chem.* **2000**, *65*, 2114.
28. Matt, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 1845.
29. Bradamate, S.; Pagani, G. A. *J. Org. Chem.* **1980**, *45*, 114.
30. Highet, R. J.; Highet, P. F. *J. Org. Chem.* **1965**, *30*, 902.