Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Parallel Synthesis in an EOF-based Micro Reactor

Charlotte Wiles and Paul Watts

The reactor described herein was fabricated using a standard photolithographic wet-etching technique, followed by thermal annealing of a cover plate (1.7 cm x 2.5 cm x 2.5 cm) to afford a sealed micro reactor.[1] The resulting micro reactor channels were profiled using an imaging technique developed by Broadwell and co-workers[2] and were found to be 280 μm (wide) x 90 μm (deep) x 2.0 cm (long). The micro channels were spaced 0.5 cm apart, to ensure the formation of a good thermal bond upon annealing. In order to mobilise reagents by EOF, platinum electrodes (0.5 mm o.d. x 2.5 cm) were placed within each of the reagent reservoirs and voltages applied using a Paragon 3B high voltage power supply (HVPS), capable of applying 0 to 1000 V to four outputs (Kingfield Electronics, UK). Automation of the HVPS using an in-house LabVIEW^{TM} program allowed, where necessary, complex sequences of voltages to be applied. For comparative purposes, voltages are reported as applied fields (V cm^{-1}) *i.e.* voltage/micro channel length; typical applied fields ranged from 200 to 50 V cm^{-1} (flow rates of 1.6 to 0.5 μl min^{-1}). The total volume of the flow reactor was calculated to be 0.5 μl; therefore when operating the reactor at flow rates in the range of 1.6 to 0.5 μl min^{-1} contact times of between 19 and 60 s.

To monitor the progress of a reaction, experiments were conducted over a period of 10 min, after which the contents of each product reservoir was analysed, in this case, by GC-MS (Varian GC (CP-3800) coupled to a Varian MS (Saturn 2000) with a CP-Sil 8 (30 m) column (Zebron-ZB5, Phenomenex) and ultra high purity helium (99.999%, Energas) carrier gas). Samples were analysed using the following method; injector temperature 250 °C, helium flow rate 1.0 ml min^{-1}, oven temperature 50 °C for 4 min and then ramped to 270 °C at 30 C min^{-1}, with a 3.0 min filament delay. Comparison of the proportion of product with respect to residual starting material enabled the progression of the reaction to be determined *i.e.* % conversion (Figure A and B).

To optimise a process, reactions were firstly conducted at 200 V cm^{-1} (1.6 μl min^{-1}) and if upon analysis of the reaction products residual starting material remained, the voltage was reduced by 10 V cm^{-1}, in order to increase the reagent residence time, this process was repeated until the maximum conversion to product was obtained. Once optimised, micro reactions were performed for 2.5 hr, upon which the reaction products are concentrated *in vacuo* and the yield recorded, prior to dissolution in $CDCl_3$ and analysis of the 'crude' material by NMR spectroscopy (Jeol GX400).

Preparation of silica-supported sulfonic acid 3: Silica gel (1.00 g, Kielselgel 60, sieved to 37-42 μm particles) was added to a stirred solution of (3-mercaptopropyl)-trimethoxysilane (0.49 ml, 2.50 mmol) in dry toluene and heated to reflux under nitrogen for 24 hrs. The resulting reaction mixture was concentrated *in vacuo* to remove any residual (3-mercaptopropyl)-trimethoxysilane prior to filtering the functionalised material under suction and washing with toluene (1 x 50 ml) and DCM (1 x 50 ml). The resulting thio-functionalised silica gel was resuspended in methanol (10.00 ml) and oxidised using hydrogen peroxide (5.00 ml, 100 volumes). After 24 hrs, the sulfonic acid functionalised silica gel **3** was filtered under suction, washed with water (1 x 50 ml) and acetone (1 x 50 ml) prior to drying in an oven (60 °C).

Determination of functionalisation: In order to determine the loading of sulfonic acid prepared, a portion of functionalised silica gel **3** (0.10 g assuming 2.5 mmol g^{-1}) was suspended in an aqueous solution (5 ml) of potassium permanganate (0.047 g, 3.0 mmol). The resulting reaction mixture was stirred for 24 hrs, filtered under suction and washed with deionised water (3 x 50 ml) and acetone (2 x 50 ml), then dried in an oven (60 °C). The above procedure was repeated using unfunctionalised silica gel, enabling a blank determination to be made. The resulting solid was digested in nitric acid (1.0 ml, Romil SpA grade) and the resulting digests diluted with water (Elga UHQ grade) and the supernatant analysed by ICP-MS at 257.61 nm, whereby a loading of 2.49 mmol g^{-1} was confirmed.

Batch reactor protocol: Silica-supported sulfonic acid **3** (0.10 g, 0.25 mmol) was added to a mixture of alcohol (5.00 mmol) and 3,4-dihydro-2*H*-pyran (5.00 mmol) in MeCN (5 ml). The reaction mixture was stirred at room temperature for a period of 24 hr, after which the catalyst was removed by filtration and washed; the combined washings were concentrated *in vacuo* to afford the respective THP ether.

Micro reactor protocol for the synthesis of THP ethers: To synthesise an array of THP ethers under continuous flow conditions, a pre-mixed solution of 3,4-dihydro-2-pyran **1** and alcohol (1.0 M respectively) in MeCN was placed in reservoir A and mobilised through the packed-bed (1 mg of supported catalyst channel^{-1}) by application of a voltage (200 to 400 V) and the reaction products collected at the common ground (0 V) in MeCN (40 μl). After 10 min, the reaction products were analysed by GC-MS to determine the % conversion of alcohol to THP ether. Once the flow rate, and hence conversion, was optimised, the reactors were operated for 2.5 hrs and the reaction products collected and concentrated *in vacuo* to remove the reaction solvent. The yield of the resulting residue was recorded prior to dissolution in $CDCl_3$ and analysis by NMR spectroscopy, to confirm product purity. To prevent contamination, the micro reactor was purged, under electroosmotic flow (1000 V, 5.00 μl min^{-1}), with MeCN for 10 min between reactions. Figure C illustrates the reaction set-up used when screening catalysts.

Micro reactor protocol for the deprotection of THP ethers: Deprotection of THP ethers is achieved *via* dissolution in MeOH (1.0 M) and mobilisation of the resulting solution through a packed-bed (1 mg of supported catalyst channel^{-1}) by application of a positive voltage (400 V). The reaction products were collected at the common ground (0 V) in MeOH (40 μl), samples were taken every 10 min and analysed by GC-MS. Once optimised, the reactor was operated for 2.5 hr, the reaction products collected and concentrated *in vacuo* to remove the reaction solvent and 2-methoxy-tetrahydropyran **5**. Comparison of the GC retention times and mass spectra of deprotected products with commercially available alcohols enabled structural confirmation. To prevent contamination, the micro reactor was purged, under electroosmotic flow (1000 V, 5.00 μl min^{-1}), with MeCN for 10 min, between reactions.

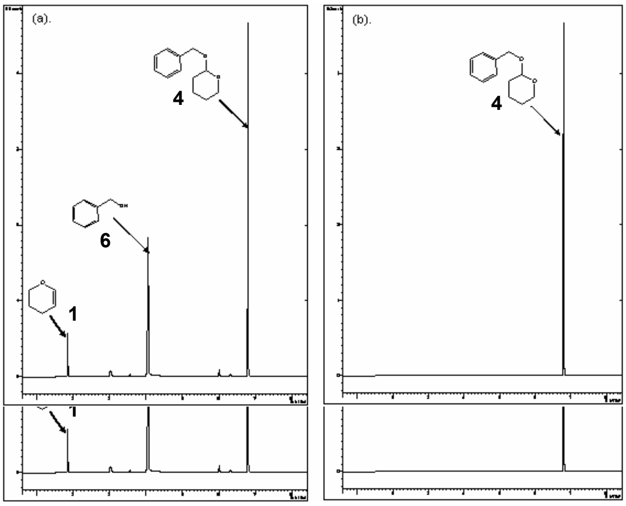


Figure A. Gas chromatograms illustrating the synthesis of THP ether **4** conducted under [a]. batch (24 hrs) and [b]. continuous flow (1.50 μl min^{-1}) conditions.

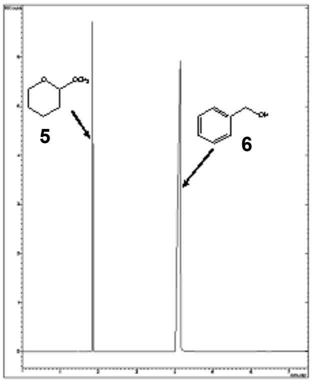
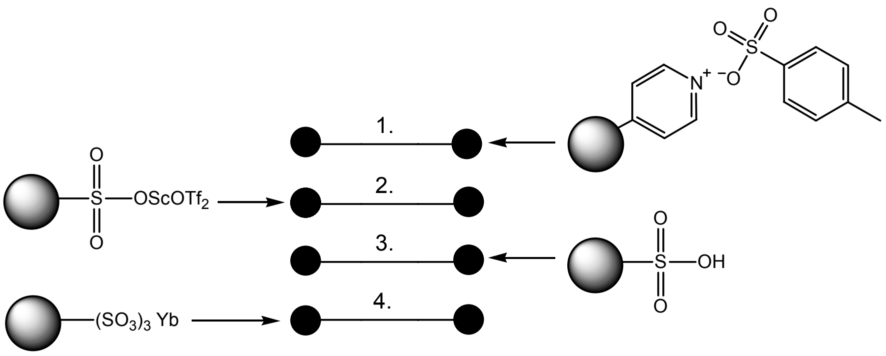


Figure B. Chromatogram illustrating the efficient depyranylation of 2-benzyloxy-tetrahydropyran **4** to afford benzyl alcohol **6** and 2-methoxy-tetrahydropyran **5**.



Channel 1. 1.10 µl min^{-1}, 100.0 %, Channel 2. 1.60 µl min^{-1}, 99.9 %
Channel 3. 1.80 µl min^{-1}, 100.0 %, Channel 4. 1.50 µl min^{-1}, 99.9 %

Figure C. Reaction set-up used to evaluate an array of solid-supported acids for the synthesis of 2-benzyloxy-tetrahydropyran **4**.

[1] T. McCreedy, *Anal. Chim. Acta,* **2001**, 201, **427**, 39-43.

[2] I. Broadwell, P. D. I. Fletcher, S. J. Haswell, T. McCreedy, X. Zhang, *Lab Chip*, **2001**, *1*, 66-71.