Parallel synthesis in an EOF-based micro reactor†

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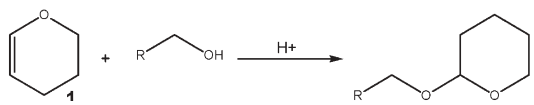
We present herein a micro reactor set-up that enables parallel syntheses to be performed under electroosmotic flow conditions.

The last decade has seen an array of synthetic transformations performed within micro fabricated reactors,[1] to date however none of the systems developed have described the scale-out[2] of reactions conducted under electroosmotic flow (EOF),[3] or those employing solid-supported reagents and catalysts. In order to achieve the goal of synthesising analytically pure compounds within microfabricated reactors, we recently described the incorporation of supported reagents and catalysts into capillary based flow reactors, largely employing EOF as the pumping mechanism.[4] Although this approach enabled the synthesis of numerous compounds without the need for additional off-line[5] or in-line[6] purification, the quantities of material produced (<10 mg h^{-1}) were not suitable for the target markets, which include both the fine chemical and pharmaceutical industries. To address this shortfall, we began investigating means of increasing the quantity of material synthesised, whilst retaining those advantages previously obtained as a result of reaction miniaturisation. We present herein our initial evaluation of a micro reactor capable of performing four parallel reactions under EOF, employing the synthesis of tetrahydropyranyl (THP) ethers as a model reaction.

THP ethers have found widespread use as protecting groups for both aromatic and aliphatic alcohols, largely owing to their stability to strongly basic, acylating, alkylating and organometallic reagents, but also the facile nature of their deprotection.[7] In addition, THP ethers can undergo a series of reactions including oxidative deprotection, enabling the rapid conversion of an alcohol to its respective carbonyl derivative.[8] As illustrated in Scheme 1, THP ethers are synthesised *via* the acid catalysed reaction of an alcohol with 3,4-dihydro-2*H*-pyran **1** (DHP) (>1 eq.); a protocol which affords THP ethers in yields ranging from 57 to 97%.[9] The main disadvantage of the technique however is the need to purify the resulting THP ethers in order to remove excess DHP **1**,[9a] any unreacted starting materials and the acid catalyst. In addition, extreme reaction conditions can often be required, such as elevated reaction temperatures, which in a process environment leads to accelerated corrosion of reactor vessels and the generation of acidic waste water. To some extent this shortfall has been addressed by the application of solid-supported acids, such as Nafion-H,[9b] Zeolite H-beta,[10] poly(4-vinylpyridinium *p*-toluenesulfonate)[9c] and silica-supported perchloric acid,[9d] which allows the catalyst to be readily separated from the reaction products by filtration. Reaction times however remain in the order of hours and the techniques reported still require excess DHP **1** in order to obtain good yields.



Scheme 1 General reaction protocol employed for the protection of alcohols as their respective THP ether.

With these factors in mind, we proposed that reaction efficiency could be improved by conducting tetrahydropyranylations under continuous flow conditions, not only enabling the use of stoichiometric quantities of DHP **1**, but also affording reduced reaction times. In addition, this mode of operation facilitates efficient recycle of the supported catalyst, whilst ensuring no acidic waste is generated. Although previous reactors have allowed us to evaluate the feasibility of conducting polymer and silica-assisted reactions under electroosmotic conditions, the techniques employed did not lend themselves to the rapid and reproducible replication of devices that is required for mass production. We therefore sought to fabricate a micro reactor that would enable multiple reactions to be performed in parallel, selecting borosilicate glass as the reactor substrate due to its compatibility with a broad range of organic solvents, high mechanical strength, temperature resistance, optical transparency and the ability to support EOF.

As Fig. 1 illustrates, we proposed that by etching multiple reaction channels within a single base-plate, reaction throughput could be increased, whilst retaining those reaction characteristics of a single channel reactor. To construct the packed-beds, micro porous silica frits (MPSF)[11] were placed at one end of the micro channels, and once cured, the supported reagents were dry-packed into the reaction channels and a second MPSF used to retain the reagent.

Although we have previously demonstrated the use of polymer-supported acid catalysts within capillary based flow reactors,[4] owing to the large particle size of commercially available catalysts, such as Amberlyst-15 (297–1190 μm), the supported materials needed to be ground and sieved prior to use. Therefore a silica-supported sulfonic acid **3** derivative was prepared, in accordance

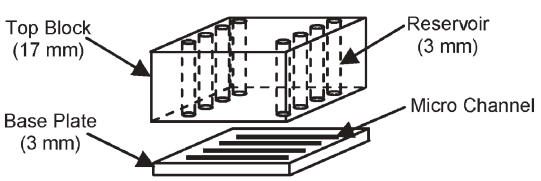


Fig. 1 Schematic illustrating an exploded view of the multi-channel reactor evaluated for the parallel synthesis of THP ethers.

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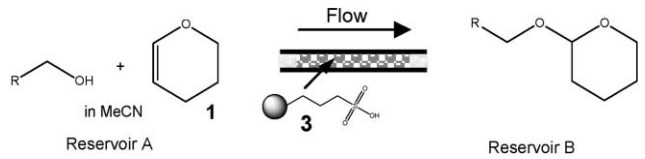

Fig. 2 Schematic illustrating the general procedure used for the synthesis of THP ethers in a packed-micro channel.

with a published protocol by Bossaert and co-workers,[12] affording a catalyst loading of 2.50 mmol g^{-1} and a particle size distribution of 38 to 45 μm, enabling reproducible packing of the micro channels.

Prior to performing a reaction, the micro channels were packed with the silica-supported sulfonic acid **3** (1 mg channel^{-1} = 2.5 × 10^{-3} mmol) and primed with anhydrous MeCN, to ensure formation of a complete circuit, enabling the mobilisation of both reagents and products by EOF. To synthesise an array of THP ethers, a pre-mixed solution of DHP **1** and alcohol (1.0 M, 1 : 1) was placed in reservoir A, mobilised through the packed-bed (containing the solid-supported acid catalyst) and the reaction products collected in reservoir B (40 μl, MeCN) (Fig. 2). After a run time of 10 min, the reaction products were removed from reservoir B and analysed off-line, by GC-MS, whereby the % conversion of alcohol to THP ether was determined (Table 1). Once optimised, the reactors were subsequently operated continuously in order to synthesise the desired quantity of material. In this case, reactions were conducted for 2.5 h in order to generate sufficient material for evaluation by NMR spectroscopy and where necessary elemental analysis.

Employing the synthesis of 2-benzyloxytetrahydropyran **4** as a model reaction, system reproducibility was firstly investigated by analysing the reaction products generated every 10 min over the course of 2.5 h. Using this approach, excellent reaction reproducibility was demonstrated (n = 15, % conversion = 99.997 and % RSD = 4.6 × 10^{-3}), confirming catalyst stability. In addition, when conducting the tetrahydropyranylations under continuous flow conditions, it was observed that a cleaner reaction product resulted, compared to that obtained from analogous batch reactions. This observation is ascribed to polymerisation of DHP **1** owing to the extended reaction times employed, typically 24 h.[13] Prior to investigating the scope of the technique, catalytic activity of the solid-supported sulfonic acid **3** was evaluated, firstly by performing the reaction in the absence of a catalyst and secondly by replacing the catalyst with silica gel (1 mg channel^{-1}). As expected, no product formation was detected in either of the blank determinations, simply unreacted starting materials; confirming that the observed reaction was attributed to the activity of silica-supported sulfonic acid **2** and not due to performing the reaction in an electric field.

Based on these observations, the generality of the technique was subsequently investigated, synthesising a further 14 THP ethers. As illustrated in Table 1, both aliphatic and aromatic alcohols were successfully protected using the same reaction conditions along with molecules containing sensitive functional groups, this is illustrated by the protection of (*E*)-3-phenylprop-2-en-1-ol, whereby no isomerism was observed. In addition to the observed increased reaction efficiency, a further advantage of flow reaction methodology is the ease with which catalysts can be recycled, this is illustrated herein whereby 6.9 mmol of product was synthesised using 2.5 × 10^{-3} mmol of catalyst, affording a turnover number of 2760.

Along with efficient introduction, an important facet of protecting group chemistry is the ability to remove the blocking group once it has served its function. Consequently, the next step of our investigation was to evaluate the deprotection of THP ethers under continuous flow conditions. As observed for the tetrahydropyranylations, many different reaction conditions have been reported to effect depyranylation, all techniques however are acid catalysed[14] and proceed *via* a hydrolysis or alcoholysis pathway.[15] The method described herein employs MeOH as the reaction solvent, which enables depyranylation to be monitored not only by detection of the desired alcohol but also by the formation of the alcoholysis product, 2-methoxytetrahydropyran. Using this approach, a solution of THP ether (1.0 M in MeOH) is simply mobilised through the catalyst bed, where depyranylation occurs, to afford the respective alcohol. As 2-methoxytetrahydropyran is readily removed *in vacuo*, optimisation of the reagents residence time, to afford complete deprotection, provides an efficient, high yielding route to alcohols (Table 2).

Table 1 Summary of the results obtained for the protection of numerous alcohols as their respective THP ether in a single channel, employing a residence time of 19–20 s

Tetrahydropyran derivative	Flow rate/μl min^{-1}	Conv.[a] (%)	Yield[b]/g
2-Benzyloxy- (**4**)	1.50	99.9 (4.6 × 10^{-3})	0.0432 (99.9)
2-Butoxy-	1.50	99.9 (3.5 × 10^{-4})	N/A[c]
2-Hexyloxy-	1.50	100.0 (0.0)	0.0627 (99.8)
2-Octyloxy-	1.50	99.9 (2.6 × 10^{-4})	0.0720 (99.7)
2-Decyloxy-	1.50	99.9 (2.6 × 10^{-4})	0.0812 (99.8)
2-Cyclohexyloxy-	1.40	99.9 (3.5 × 10^{-4})	0.0579 (99.9)
2-(2-Methylcyclohexyl-oxy)-	1.40	100.0 (0.0)	0.0415 (99.8)
2-(1-Phenylpropoxy)-	1.40	99.9 (3.5 × 10^{-4})	0.0461 (99.8)
2-(4-Bromobenzyloxy)-	1.50	99.9 (5.9 × 10^{-4})	0.0608 (99.7)
2-(4-Chlorobenzyloxy)-	1.50	99.9 (3.5 × 10^{-4})	0.0508 (99.9)
2-(4-Aminobenzyloxy)-	1.50	100.0 (0.0)	0.0438 (99.8)
2-(3-Phenylallyloxy)-	1.50	99.9 (5.9 × 10^{-4})	0.0487 (99.4)
2-(Naphthalen-2-yloxy)-	1.50	99.9 (4.6 × 10^{-4})	0.0511 (99.6)
2-Benzhydryloxy-	1.60	100.0 (0.0)	0.0643 (99.9)
2-Phenoxy-	1.30	100.0 (0.0)	0.0346 (99.7)

The number in parentheses represents the [a] % RSD where n = 15 and [b] % isolated yield, after removal of the reaction solvent *in vacuo*. [c] Due to volatility of the resulting alcohol, an isolated yield was not recorded.

Table 2 Summary of the results obtained for the deprotection of THP ethers under continuous flow (single channel, residence time = 20 s)

Alcohol	Flow rate/ μl min^{-1}	Conv. (%)	Yield[a]/g
Benzyl alcohol	1.50	100.0	0.0241 (99.2)
Butan-1-ol	1.50	100.0	N/A[b]
Hexan-1-ol	1.50	100.0	0.0229 (99.6)
Octan-1-ol	1.50	100.0	0.0292 (99.7)
Decyl alcohol	1.50	100.0	0.0355 (99.7)
Cyclohexanol	1.50	100.0	0.0223 (99.1)
Methylcyclohexanol	1.50	100.0	0.0256 (99.6)
1-Phenylethanol	1.50	100.0	0.0274 (99.6)
4-Bromobenzyl alcohol	1.50	100.0	0.0420 (99.8)
4-Chlorobenzyl alcohol	1.50	100.0	0.0319 (99.4)
4-Aminobenzyl alcohol	1.50	100.0	0.0276 (99.6)
3-Phenylprop-2-en-1-ol	1.50	100.0	0.0301 (99.7)
2-Naphthol	1.50	100.0	0.0322 (99.4)
Benzhydrol	1.50	100.0	0.0414 (99.9)
Phenol	1.50	100.0	0.0210 (99.2)

[a] The number in parentheses represents the % isolated yield, after removal of the reaction solvent *in vacuo*. [b] Due to volatility of the resulting alcohol, an isolated yield was not recorded.

Table 3 Summary of the results obtained for the synthesis of 2-benzyloxytetrahydropyran **4**, using an array of solid-supported acid catalysts[a]

Supported Lewis acid	Loading/ mmol g^{-1}	Flow rate/ μl min^{-1}	Conv. (%)
Pyridinium toluene-4-sulfonate	3.50	1.10	100.0 (0.0)[b]
Scandium trifluoromethane sulfonate	0.60	1.60	99.9 (3.5×10^{-4})
Amberlyst-15 **2**	4.20	1.80	100.0 (0.0)
Ytterbium polystyryl sulfonate	2.00	1.50	99.9 (2.6×10^{-4})

[a] Alcohol (1.0 M), DHP **1** (1.0 M) and MeCN as solvent. [b] The number in parentheses represents the % RSD, where $n = 15$.

Having demonstrated the synthesis of an array of THP ethers in excellent yield and purity, and their subsequent deprotection, the next step was to investigate the scale-out of the technique *via* parallel synthesis. Again, employing the synthesis of 2-benzyloxytetrahydropyran **4** as the model reaction, all four reaction channels were operated in parallel, under the previously optimised reaction conditions (Table 3).

Using this approach, a throughput of 50 mg h^{-1} was obtained, compared with the 12.5 mg h^{-1} from a single channel reactor. To ensure reactor stability was maintained over multiple channels, the reaction products were again monitored regularly by GC-MS, confirming reproducibility over the entire device ($n = 60$, % RSD = 5.48×10^{-4}). In addition to the obvious increase in productivity achieved using the reaction set-up described, this approach also provides system flexibility, enabling the optimisation of multiple reactions in parallel or catalyst screening.

In summary, using the protection of alcohols as a model reaction we have described a simple, efficient and robust technique for the scale-out of micro reactions conducted under EOF conditions, employing solid-supported reagents and catalysts. This study therefore aids in realising the potential of electroosmotic flow as a pumping mechanism for the production of fine chemicals and pharmaceuticals. Further development of such parallel reaction systems is however required in order to synthesise the quantities of material required for large-scale production. Employing the aforementioned technology, 15 THP ethers were synthesised in near quantitative yield and excellent purity, without competing DHP **1** polymerisation (which is frequently observed in batch reactions), along with quantitative depyranylation when MeOH was used as the reaction solvent.

In addition, through the incorporation of supported catalysts into such miniaturised packed-beds, efficient catalyst recycle is achieved without the need to filter, wash and recover catalytic material between reactions. Based on the investigation presented herein, the silica-supported sulfonic acid derivative **2** afforded a turn over in excess of 2760 times, showing no sign of degradation to date. Furthermore, the system flexibility described enables the reactor to be employed, as a means of increasing the production capacity of a micro reaction, whilst also enabling the same reactor set-up to be used for catalyst or reagent screening; with minimal reagent or catalyst investment. Further work is currently underway into ways of increasing throughput of such reactors, along with their application to more complex reactions systems.

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