Application Note 7.3

Swern-Moffatt oxidation

The Swern-Moffatt oxidation is a highly valuable reaction, as it selectively oxidises alcohols to the corresponding aldehydes or ketones. In batch, the reaction requires a temperature of -78°C. The reaction was successfully scaled out to a preparative scale in the *Flow*Syn microreactor platform, thereby continuously producing 8.5 g/hr of the desired product.

Future Chemistry

Introduction

The Swern-Moffatt oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones is a useful reaction in organic chemistry, as it provides a selective pathway towards aldehydes and ketones. This reaction is difficult to control due to its fast reaction rate and exothermic character, and is therefore traditionally performed at -78°C. At elevated temperatures, side product formation becomes dominant, except when very short reaction times are used. These short reaction times can be perfectly controlled in a continuous flow microreactor.
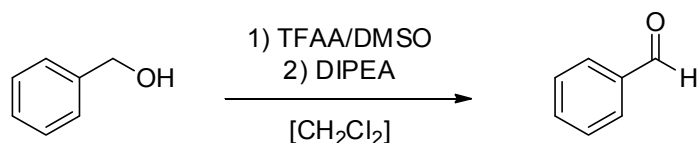

Figure 1: Swern-Moffatt oxidation of benzyl alcohol

To avoid the use of low temperatures and controlled reagent addition, FutureChemistry has translated this reaction from a batch process to a continuous flow process. FutureChemistry's typical three-tier approach led to a protocol which can be adapted to any viable alcohol substrate:

1) *Flow*Start. Translation of batch process to continuous flow process.
2) *Flow*Screen. Automated reaction optimisation.
3) *Flow*Syn. Out scaling to preparative synthesis:
   a) Validate previously found optimum.
   b) Scale out to preparative synthesis.

This *application note* describes the out scaling of the continuous flow process using the *Flow*Syn.

Reaction out scaling

Up scaling of batch processes traditionally poses a variety of problems, since heat conduction and mixing greatly differs with reactor size. In batch chemistry, small-scale reactions are usually conducted by organic chemists while large-scale reactions are performed by chemical engineers. Using flow chemistry, out scaling is a one-to-one process in most cases, eliminating the need for a different viewpoint on reaction conditions and practical concerns between small-scale and large-scale.

Optimal reaction conditions for the Swern-Moffatt oxidation were found using the *Flow*Start, and were slightly adapted to the *Flow*Syn. The reaction was conducted at a **temperature of 20°C, TFAA/alcohol stoichiometry of 3.0 and reaction time of 3.3 seconds**. Quenching was done using the additional *Flow*Syn pump module.
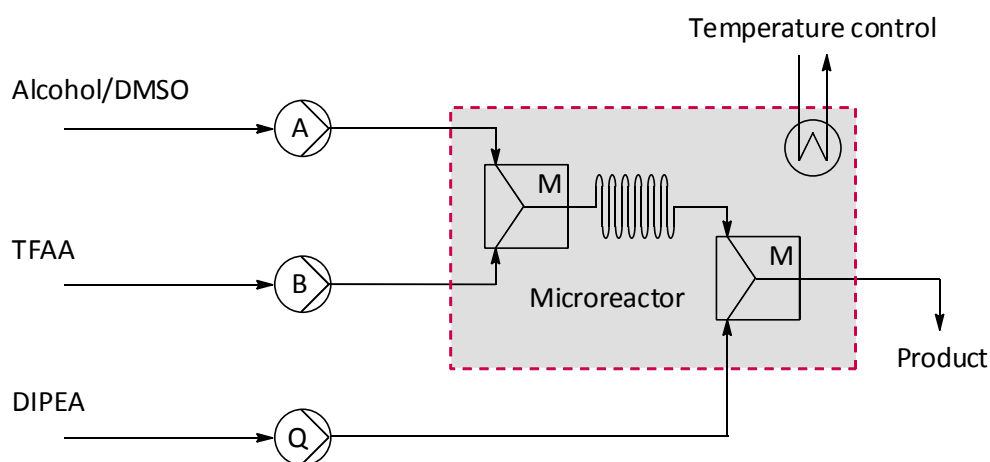

Figure 2: *Flow*Syn setup.

Preparative synthesis of the target compound benzaldehyde at the above optimum with the setup depicted in Figure 2 resulted in the **continuous production** at an **8.5 g/hr** rate, which can easily be scaled out to higher rates by using a larger reactor.

Method

All experiments were conducted in a standard FutureChemistry *Flow*Syn setup, using the *Flow*Syn Quench Microreactor with an internal volume of 0.65 mL.

Solution A (0.25 M):   Benzyl alcohol (2.58 mL, 25.0 mmol) and dimethyl sulfoxide (16.0 mL, 175 mmol) dissolved to a total volume of 100 mL with dichloromethane

Solution B (0.75 M):   Trifluoroacetic anhydride (10.5 mL, 75.0 mmol) dissolved to a total volume of 100 mL with dichloromethane

Solution Q (neat):   Di*iso*-propylethylamine

Three flasks were filled with solutions A, B and Q. Pump rates were set to 6.0, 6.0 and 1.5 mL/min respectively. The experiment was stabilised for 2 min, then run for 14 min. The product mixture was washed with 1 M HCl (3x 100 mL) and brine (100 mL), dried, filtered and solvent removed. The crude product was distilled under reduced pressure, collecting the fraction coming over at 20 mbar and 62°C. This fraction was dissolved in 100 mL *n*-heptane and stirred vigorously with 100 mL 0.5 M NaOH for 0.5 hr. The organic layer was dried, filtered and solvent removed to yield 1.98 g of benzaldehyde in an 89% yield (GC analysis shows a significant amount of heptane).

Note: The work-up procedure can probably be improved on by using pentane in the last step, and using larger amounts for the distillation.