Swern-Moffatt oxidation in a continuous flow microreactor

Background

The Swern-Moffatt oxidation is an adaptation of the Swern oxidation, and selectively oxidises an alcohol to the corresponding aldehyde or ketone. The reagent is a system comprised of dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride (TFAA), which forms an active species able to oxidise the alcohol. Hünig's base (diiso-propylethylamine; DIPEA) is used for the final step in the reaction and as a quenching agent to stop the reaction.

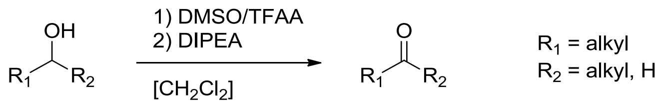

Figure 1: Swern-Moffatt oxidation scheme

Using batch chemistry, the Swern-Moffatt oxidation is performed at -80°C. This low temperature is needed to control the reaction, which is highly exothermic and extremely fast. Using continuous flow chemistry, the contact time of the reagents can be very short and precisely controlled, and the reaction can be performed at temperatures between 0°C and 60°C.

Setup and method

Material

- *Flow*Start B-200
- B-230 Pump Module
- B-242 Inlet Module
- B-248 Gas tight glass syringe (1 mL, high grade)
- Short Quench Microreactor (internal volume $V_{\mu R}$ = 1.0 µL)

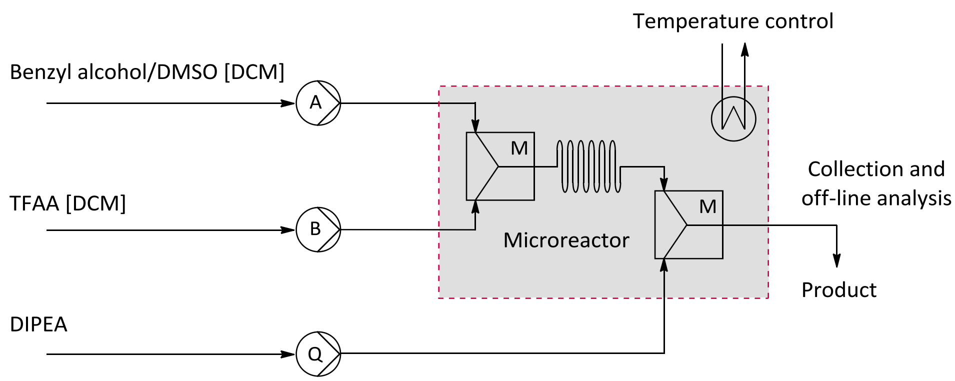

Figure 2: FlowStart setup for the Swern-Moffatt oxidation

Chemicals

Recommended grade: *pro analysi* (p.a.) or *reagent grade*.

- dimethyl sulfide (DMSO)
- trifluoroacetic anhydride (TFAA)
- benzyl alcohol

- diiso-propylethylamine (DIPEA)
- dichloromethane (DCM)
- cyclooctane (used as internal standard)

Stock solutions

A. 207 µL benzyl alcohol (2.00 mmol), 268 µL cyclooctane (2.00 mmol), 1.29 mL DMSO (18.0 mmol) dissolved to a total volume of 10 mL with DCM (corresponding to 0.2 M)

B. 1.67 mL TFAA dissolved to a total volume of 10 mL with DCM (corresponding to 1.2 M)

Q. DIPEA (neat) (corresponding to 6.0 M)

Stock solutions are to be prepared at the beginning of the experiments. Make sure to close the flasks which are used to store the solutions, as some of the components are rather volatile.

Analysis

Analysis of the reaction mixture is done using gas chromatography. Calibration of the product against the internal standard (cyclooctane) is done using general methodology. For a quick calibration, make 4 samples with a fixed cyclooctane concentration and a varying compound concentration. Analyse these samples and 1) setup a calibration curve of peak area ratio against concentration ratio and/or 2) determine the relative response factor.

Basic experiment

To get acquainted with the reaction and with flow chemistry in general, a so-called *basic experiment* is performed. This experiment is the Swern-Moffatt oxidation at fixed parameters – a reaction time (t_R) of 1.0 sec, a temperature of 20°C and a trifluoroacetic anhydride (TFAA) molar excess ratio ($ME_{B/A}$) of 6.0. The Q/B molar excess ratio ($ME_{Q/B}$) is set to a fixed value of 2.0. The target volume of solution A to be collected is 50 µL and all samples are collected in a GC vial containing 500 µL DCM. The used setup can be seen in Figure 2.

The corresponding flow rates can be calculated according to the known equations. After preparation of this experiment, the instructor should check if the calculated flow rates and collection time are correct.

Procedure

- Prepare solutions A, B and Q
- Fill the three syringes with solutions A, B and Q (use the Teflon syringe for solution B)
- Slide the microreactor into the holder and connect inlet and outlet tubing
- Connect the inlet tubing to the corresponding syringes, and place the syringes on the pumps
- Set the right flow rates and press start
- Stabilise for 1.0 minutes
- Collect your sample for the calculated time
- Analyse your sample using gas chromatography and calculate product yield from the calibration curve or relative response factor
- Rinse the *Flow*Start system by purging the tubing and microreactor with acetone
- Empty, clean and dry the syringes afterwards

Note: Make sure to close the vial after collecting. This is done because some of the reaction components are rather volatile and readily evaporate from the vial.

Questions

1. **Preparation of the experiment:**
    a. **Roughly calculate the cost of the experiment from the prices of the chemicals. In other words, calculate the price (e.g. per gram) of the product.**
    b. **Find the safety aspects (including R/S values) of the used chemicals.**

2. **Q: Find the reaction mechanism for the Swern-Moffatt oxidation, and show the essential (sequential) steps from benzyl alcohol and DMSO/TFAA to the corresponding aldehyde or ketone.**

3. **Q: What advantages in performing the Swern-Moffatt oxidation in continuous flow can you think of? Also, can you think of any disadvantages?**

4. **Typically, the Swern-Moffatt oxidation produces a number of side products. Find out what they are, how they are formed, and how the formation of these products is suppressed in batch chemistry. Also try to explain why these side products are formed to a much lesser extent in continuous flow chemistry.**

5. **Flow chemistry is best carried out in a homogeneous, liquid phase (no gases, no solids). The Swern-Moffatt oxidation is an adaptation of the Swern oxidation, where oxalyl chloride is used instead of TFAA. Explain (using the first statement) why the 'regular' Swern oxidation might pose problems when performed in a flow system.**