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.
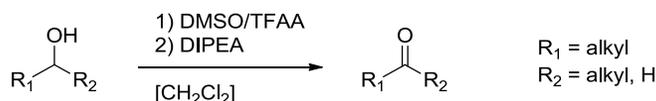

Figure 1: Swern-Moffatt oxidation scheme

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)
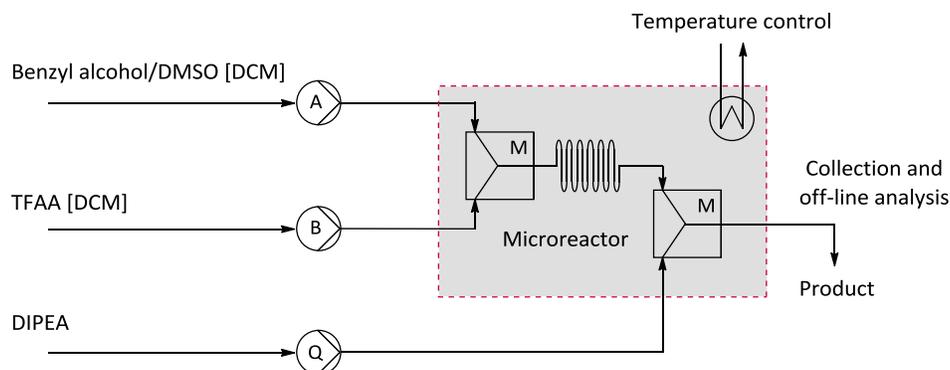

Figure 2: FlowStart setup for the Swern-Moffatt oxidation

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.

Optimisation experiment
The goal of this experiment is to identify the influence of reaction parameters on product yield and/or to find optimal reaction conditions (i.e. parameter settings) for performing the Swern-Moffatt oxidation using flow chemistry. Optimisation in a three-dimensional space can be done using various mathematical techniques, of which are commonly used: univariate analysis, full-factorial design, 3D simplex.

Flow parameters
Using flow chemistry, reaction parameters can be easily varied by adjusting the flow rates and temperature. The latter parameter speaks for itself, while both B/A molar excess ratio and reaction time are controlled by setting different flow rates. The reaction parameters and their useful ranges are listed in Table 2. Parameters should not be chosen outside these ranges, as the pump's flow rate and the substrate's boiling point impose some of these limits. Also, the reaction has been extensively screened to yield a good experimenting region within these limits.

Table 1: Reaction parameter ranges

Parameter	Minimum value	Maximum value
Reaction time (t_R)	0.3 sec	3.0 sec
TFAA/benzyl alcohol molar excess ratio ($ME_{B/A}$)	1.0	10
Temperature (T)	0°C	60°C

The stabilisation time for this reaction is two times the reaction time. 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. Quenching molar excess ratio ($ME_{Q/B}$) is fixed to 2.0. The used setup can be seen in Figure 2.

Swern-Moffatt oxidation optimisation setup
Preparation:

- Using one of the above optimisation techniques (or a different one), choose the parameter sets you want to investigate.
- For all the points in the parameter sets, calculate the flow rates and collection time. Then conduct the experiments in the same way as the introductory experiment. However, stabilisation time is changed to two times the reaction time ($t_{stab} = 2 \cdot t_R$).
- If you have obtained all measurement data and the results look valid (e.g. duplicates show the same yield), present your data graphically and find the optimal conditions to perform the Swern-Moffatt oxidation in flow.

Analysis:
- Measure the samples using gas chromatography, analyse the yield per sample, and report the obtained data in a graphical way. Also, find *optimal conditions* and/or *parameter trends* for performing the Swern-Moffatt oxidation in flow.

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.**