# Swern-Moffatt oxidation in a continuous flow microreactor

*Instructor manual*

## Introduction

In the student manual the student will find the necessary information to perform the experiments for the Swern-Mofatt oxidation. The student will investigate the Swern-Moffatt oxidation in a continuous flow microreactor. The first part of the manual will describe an introductory experiment to get acquainted with flow chemistry in general and, more specific, with this extremely fast and exothermic reaction. The second part is a small optimisation experiment which can be adapted to the student's scientific ambitions.

For this project, the aims are formulated as follows:
- The student understands the basics of flow chemistry, both the mathematical background and the general concepts.
- The student can use the analysis method in the correct way, and therefore has to understand the basics underlying this method, including gas chromatography (GC), internal standards and calibration curves.

This project can be performed by single or pairs of students, in which the latter case has the advantage of parallel experimenting and data analysis. Report of the project should in the least case consist of research goals, experiment setup, analysis results and conclusions, including a notion of the concept *optimum* or *optimal conditions*.

## 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 (di*iso*-propylethylamine; DIPEA) is used for the final step in the reaction and as a quenching agent to stop the reaction.
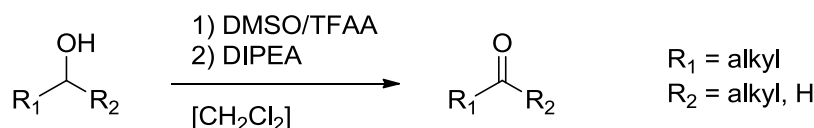


*Figure 1: Swern-Mofatt oxidation reaction mechanism*

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 highly reactive. 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.

**Note:** A complete introductory text on flow chemistry and its important relations can be found in chapter 1: Introduction to flow chemistry (page 3 – 7). Make sure the student fully understands this before starting the experiments.

## Setup and method

### Setup

- *Flow*Start B-200
- B-230 Pump Module
- B-242 Inlet Module
- B-245 Glass Syringe (with Teflon plunger)
- M-131 Short quench microreactor

### Chemicals

- Benzyl alcohol
- Cinnamyl alcohol
- 1-Phenyl ethanol
- Dimethyl sulfoxide (DMSO)
- Trifluoroacetic anhydride (TFAA)
- Cyclooctane (internal standard)
- 1-Bromonaphthalene (internal standard)
- Di*iso*-propylethylamine (DIPEA)
- Dichloromethane

### Stock solutions

A. 207 µL benzyl alcohol (2.00 mmol), 268 µL cyclooctane (2.00 mmol, internal standard), 1.29 mL DMSO (18.0 mmol) dissolved to a total volume of 10 mL with dichloromethane
B. 1.67 mL TFAA dissolved to a total volume of 10 mL with dichloromethane
Q. DIPEA (neat)
Collection fluid: dichloromethane

Stock solutions are to be prepared at the beginning of the experiments. Make sure to stopper the flasks which are used to store the solutions, as both TFAA, dichloromethane and cyclooctane are very volatile.
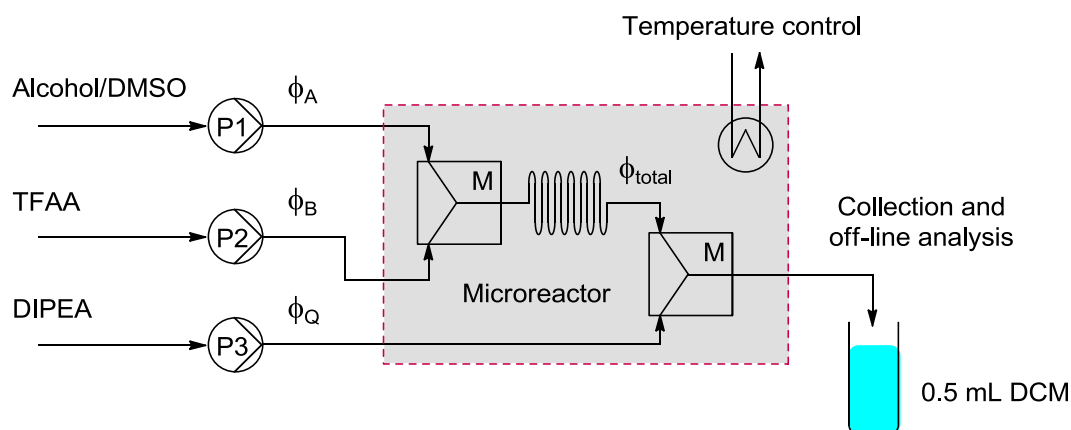


*Figure 2: FlowStart setup for the Swern-Moffatt oxidation*

### Analysis

Analysis of the reaction mixture is done using gas chromatography. Calibration of the product against the internal standard is done using general methodology. For a quick calibration, make 4 samples with a fixed cyclooctane concentration of 20 mM and a varying product concentration of 5, 10, 15 and 20 mM. Analyse these samples and 1) setup a calibration curve of peak area ratio against concentration ratio and/or 2) determine the relative response factor.

Detailed description of GC method including the temperature program for the reaction mixture and corresponding retention times of the various compounds are listed in the *Appendix: GC analysis*.

## Basic experiment

To test the reaction and to get acquainted with flow chemistry, the student performs a so-called *basic experiment*, which is defined as having a reaction time of 1.0 sec, a temperature of 20°C and a TFAA/alcohol stoichiometry of 6.0. The DIPEA/TFAA stoichiometry is set to a fixed value of 2.0. The stabilisation time for this reaction is 1.0 minute. The target volume of solution A to be collected is 50 µL, all samples are collected in a GC vial containing 500 µL dichloromethane. 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

- Make solutions A and B
- Fill three syringes with solutions A, B and Q. Make sure to use the syringe with a white plunger for the TFAA 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
- Submerge the outlet in an Erlenmeyer containing some dichloromethane and a few drops of DIPEA (this is the waste container – the DIPEA quenches any leftover reagents)
- Set the right flow rates and press start
- Stabilise for 10 minutes if this is the first run
- Collect your sample for the calculated time
- Analyse your sample using the GC and calculate yield from the calibration curve or relative response factor
- Rinse the *Flow*Start system by purging the tubing and microreactor with dichloromethane
- Empty, clean and dry the syringes afterwards

**Note:** When using cyclooctane as an internal standard, make sure to close the vial after collecting. This is done because cyclooctane, despite its high boiling point, is a very volatile compound and readily evaporates from the vial.

### Results

For the basic experiment the flow rates of A and B are 30 µL/min respectively, flow Q is 12 µL/min and the collection time is 1.40 minute. This is calculated according to the following equations:

$$\phi_{total} = \frac{V_{MR}}{t_R} = \frac{1\,\mu L}{1\,s} = 60\,\mu L \cdot min^{-1}$$

$$\phi_{total} = \phi_A + \phi_B = \phi_A \cdot \left( \frac{c_A}{c_B} \cdot S_{TFAA/alcohol} + 1 \right) \quad \text{and thus} \quad \phi_A = \phi_B = 30 \, \mu L \cdot min^{-1}$$

$$\phi_Q = \phi_B \cdot \frac{c_B}{c_Q} \cdot S_{DIPEA/TFAA} = 12 \, \mu L \cdot min^{-1}$$

$$t_{collect} = \frac{V_{target,A}}{\phi_A} = \frac{50 \, \mu L}{30 \, \mu L \cdot min^{-1}} = 1:40$$

Using the described parameter settings it is expected that a yield of around 80% will be obtained.

## Optimisation experiment

The goal of this experiment is 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 TFAA/alcohol stoichiometry and reaction time are controlled by setting different flow rates. The reaction parameters and their approximate (useful) ranges are listed in

Table *1*.

*Table 1: Reaction parameter ranges*

| Parameter | Minimum value | Maximum value |
|---|---|---|
| Reaction time | 0.3 s | 3.0 s |
| TFAA/alcohol stoichiometry | 1.0 | 10 |
| Temperature | 0°C | 60°C |

The stabilisation time for this reaction is 1.0 minute. The target volume of solution A to be collected is 50 µL, all samples are collected in a GC vial containing 0.5 mL dichloromethane. The used setup can be seen in Figure 2.

### Results of the benzyl alcohol optimisation

Preparation:

- Using one of the above optimisation techniques (or a different one), the student chooses the parameter sets he/she wants to investigate. Check if the parameter sets correspond to the useful regions stated in Table 1. Parameters should not be chosen outside these ranges, as the pump's flow rate and the solvent's boiling point impose some of these limits. Also, the reaction has been extensively screened to yield a good experimenting region.
- For all chosen points, the flow rates and collection time should be calculated. Check whether these look correct by comparing them to the standard experiment or by calculation.

Experiment:

- The student conducts the experiments in the same way as the basic experiment.

Analysis:

- The student measures the samples using GC, analyses the yield per sample, and reports the obtained data in a graphical way. Also, the student has to find *optimal conditions* for performing the Swern-Moffatt oxidation in flow.

A univariate optimisation on the full range shows the trends below. While varying one parameter, the other two are kept constant on: TFAA/alcohol stoichiometry 6.0, temperature 20°C and reaction time 1.0 s.
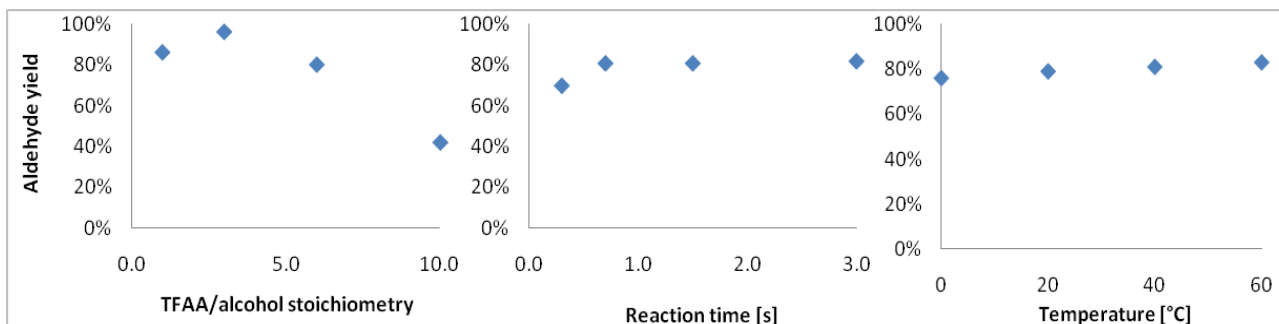


*Figure 3: Influence of stoichiometry, reaction time and temperature on yield of Aldehyde*

From this univariate optimisation it follows that yield increases linearly with temperature, but only slightly. Reaction time reaches a maximum after 0.7 s and the TFAA/alcohol stoichiometry clearly shows an optimum around 3.0. Possible *optimum conditions* are found at a TFAA/alcohol stoichiometry of 3.0, reaction time 1.0 s and 20°C.

## Optimisation of other alcohol substrates

The following experiment is the optimisation of the Swern-Mofatt oxidation using different alcohol substrates. This can be a primary and a secondary alcohol, benzylic or aliphatic. Apart from benzyl alcohol, cinnamyl alcohol and 1-phenyl ethanol were tested and found to be good substrates.

The procedure is inherently the same as the optimisation of the benzyl alcohol, with the added ability to compare the reaction behaviour while using different substrates. Check if the student has found differences between substrates, and if he/she can account for this, referencing the reaction mechanism and/or the nature of the substrate (primary/secondary, benzylic/aliphatic).

**Cinnamyl alcohol.** The optimisation results for cinnamyl alcohol follows the same trends as the benzyl alcohol univariate screening, except for a somewhat lower overall yield.

**1-Phenyl ethanol.** The optimisation results for 1-phenyl ethanol show different trends. Firstly, the optimal stoichiometry (around *basic experiment* parameters) lies at approximately 5. Secondly, there is a somewhat more pronounced temperature effect, with an optimum around room temperature. The results of this univariate analysis are plotted in Figure 4.
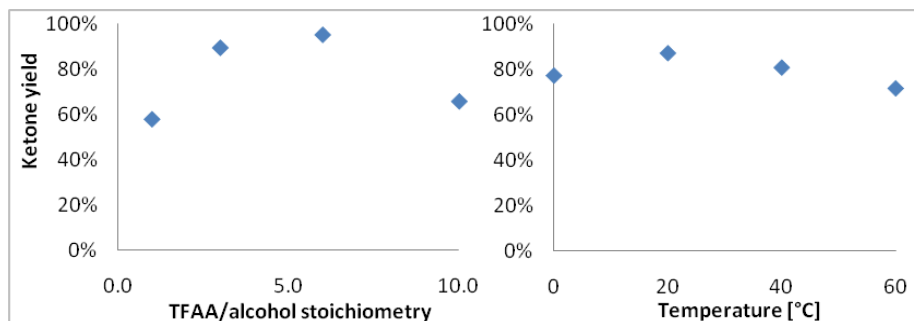


*Figure 4: Influence of stoichiometry and temperature on yield of Ketone*

*Practical Course - Swern-Moffatt Oxidation*

## Answers to the questions

1. **Find the reaction mechanism for the Swern-Moffatt oxidation, and show the essential (sequential) steps from alcohol to aldehyde/ketone. Also show where in the microreactor these steps are performed in the continuous flow setup.** The essential steps are: a) formation of the oxidative sulfonium species from TFAA and DMSO, b) addition of the alcohol, c) proton abstraction by a tertiary amine base. In flow, step a) and b) are performed at once, when the reagents are mixed in the microreactor. After reacting, two steps are again performed at once: step c) and quenching of TFA(A).

2. **For all three substrates, find the products after oxidation.** These are: benzyl alcohol → benzaldehyde, cinnamyl alcohol → cinnamaldehyde, 1-phenyl ethanol → acetophenone.

3. **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.** Side products: the trifluoroacetyl ester and thiomethyl ether, both (typically) formed at high temperatures.

4. **What advantages in performing the Swern-Moffatt oxidation in continuous flow can you think of? Also, can you think of any disadvantages?** Advantages: a) By decreasing the contact time of the reagents, the formation of side products is largely suppressed. b) Perform synthesis at elevated temperatures, due to the fact that the microreactor has an increase heat transfer in relation to a batch process. Disadvantages: a) in the current setup it is not possible to vary the DMSO/alcohol stoichiometry by controlling flow rates, b) for every substrate, the reaction has to be tested for homogeneity and (more general) viability.

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 why the 'regular' Swern oxidation might pose problems when performed in a flow system.** In the 'regular' Swern oxidation, gas (CO) is liberated. This makes the determination of reaction time much more difficult, since it is never exactly known how much fluid resides in the microreactor at a certain moment.

# Appendix: GC analysis

## Calibrations
*Used for all three alcohol substrates*

To measure percentage yield of the formed product, a calibration is set up of the desired product against an internal standard. For each substrate, use the internal standard/product combination as in Table *2*, using the concentrations from Table *3*.

*Table 2: Internal standard/product combination for each substrate*

| Substrate | Internal standard | Product |
|---|---|---|
| **Benzyl alcohol** | Cyclooctane | Benzaldehyde |
| **Cinnamyl alcohol** | 1-Bromonaphthalene | Cinnamaldehyde |
| **1-Phenyl ethanol** | Cyclooctane | Acetophenone |

*Table 3: Calibration samples for all three analysis methods*

| Sample | Internal standard | Product | Corresponding yield |
|---|---|---|---|
| **1** | 20 mM | 20 mM | 100% |
| **2** | 20 mM | 15 mM | 75% |
| **3** | 20 mM | 10 mM | 50% |
| **4** | 20 mM | 5 mM | 25% |

## Program 1

*Used for the analysis of benzyl alcohol and 1-phenyl ethanol experiments*

GC analysis was performed on a Shimadzu GC 2010 GC-FID equipped with a Quadrex 007 1701 column (length: 10 m, internal diameter: 0.1 mm, film thickness: 0.1 mm).

*Table 4: GC program used for the analysis of benzyl alcohol and 1-phenyl ethanol samples*

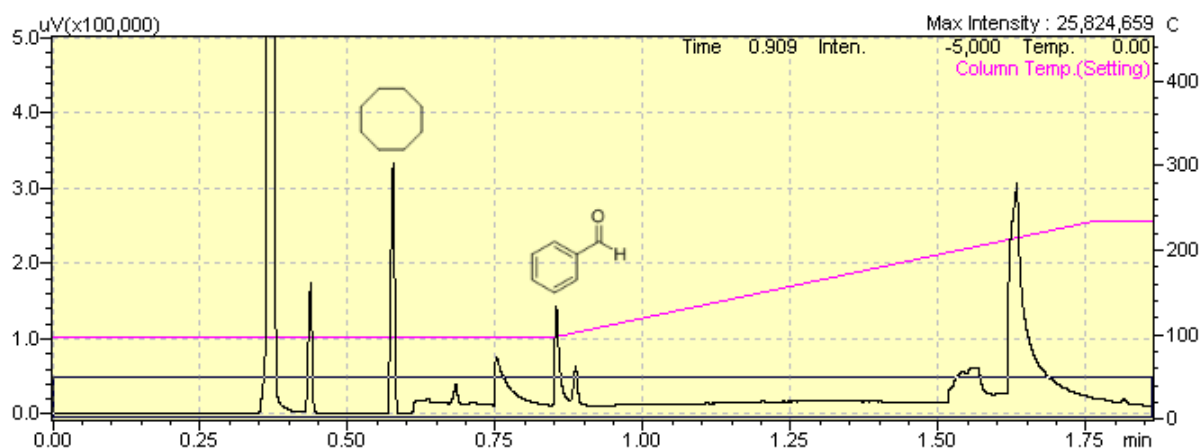| Parameter | Value | Parameter | Value |
|---|---|---|---|
| Injection volume | 1.0 µL | Split temperature | 300°C |
| | | Pressure | 5.0 bar |
| Temperature program | | Total flow | 400 mL/min |
| 0.0 – 0.85 min | 98°C | Column flow | 1.3 mL/min |
| 0.85 – 1.76 min | 150°C/min | Purge flow | 1.5 mL/min |
| 1.76 – 1.86 min | 235°C | | |



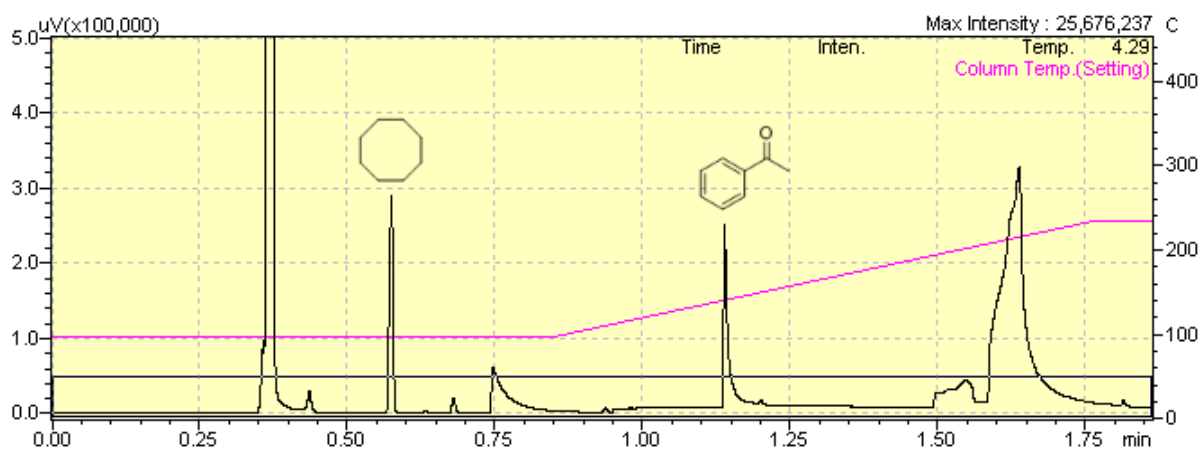*Figure 1: Example of benzyl alcohol experiment*



*Figure 2: Example of 1-phenyl alcohol experiment*

*Table 5: Retention times of internal standard and products*

| Compound | Function | Retention time [min] |
|---|---|---|
| Cyclooctane | internal standard | 0.58 |
| Benzaldehyde | product | 0.85 |
| Acetophenone | product | 1.15 |

## Program 2
### Used for the analysis of cinnamyl alcohol experiments

GC analysis was performed on a Shimadzu GC 2010 GC-FID equipped with a Quadrex 007 1701 column (length: 10 m, internal diameter: 0.1 mm, film thickness: 0.1 mm).

Table 6: GC program used for the analysis of cinnamyl alcohol samples

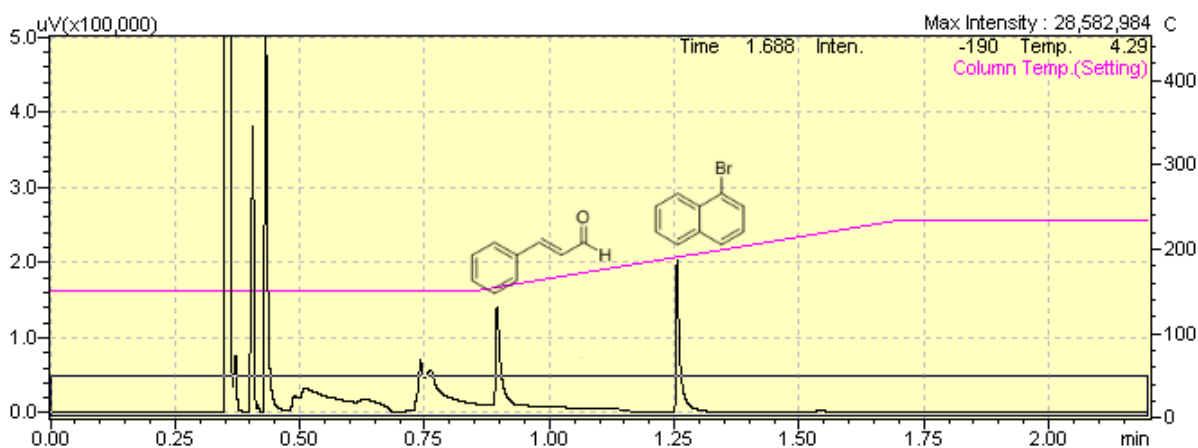| Parameter | Value | Parameter | Value |
|---|---|---|---|
| Injection volume | 1.0 µL | Split temperature | 300°C |
| | | Pressure | 5.5 bar |
| Temperature program | | Total flow | 380 mL/min |
| 0.0 – 0.85 min | 150°C | Column flow | 1.25 mL/min |
| 0.85 – 1.70 min | 100°C/min | Purge flow | 1.5 mL/min |
| 1.70 – 1.80 min | 235°C | | |



Figure 3: Example of cinnamyl alcohol experiment

Table 7: Retention times of internal standard and products

| Compound | Function | Retention time [min] |
|---|---|---|
| Cinnamaldehyde | product | 0.90 |
| 1-Bromonaphthalene | internal standard | 1.25 |