Prilezhaev epoxidation in a continuous flow microreactor

Background

The synthesis of epoxides is a useful reaction in organic chemistry, as it provides a good pathway towards trans-diols through alkaline hydrolysis. Traditionally, this reaction is difficult to control due to its fast reaction rate and exothermic character. In batch, temperature runaway is largely overcome by controlled reagent addition and the use of milder epoxidation reagents such as *meta*chloro-peroxybenzoic acid (*m*CPBA), whose synthesis again requires the use of a peroxy compound and are thus less atom-efficient.

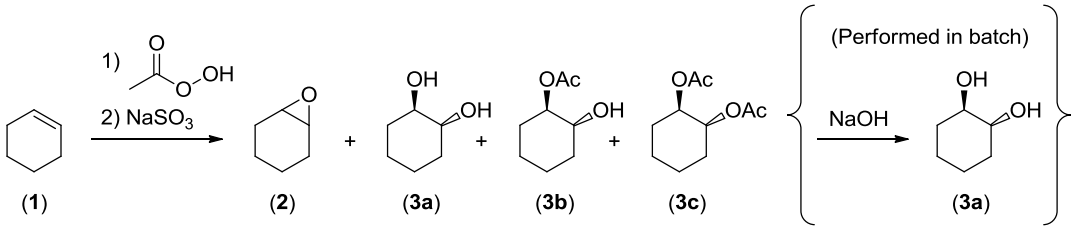

Figure 1: Prilezhaev epoxidation scheme

Epoxidation with peracetic acid poses its limits to batch scale-up, but has been shown to be possible in continuous flow. The latter has the added advantage of handling all toxic and corrosive reagents inside a closed system. In continuous flow, peracetic acid and cyclohexene (1) are introduced into the microreactor, where they react to form a mixture of the corresponding epoxide (2) and the ring-opened products which are either free diol (3a), mono-acetylated diol (3b) or di-acetylated diol (3c). This mixture of four compounds can be hydrolysed in batch by treatment with aqueous sodium hydroxide to yield only the diol (plus any unreacted cyclohexene).

Setup and method

Material

- *Flow*Start B-200
- B-230 Pump Module
- B-242 Inlet Module
- 3x plastic 10 mL syringe
- Basic Quench Microreactor (internal volume $V_{\mu R}$ = 92 µL)

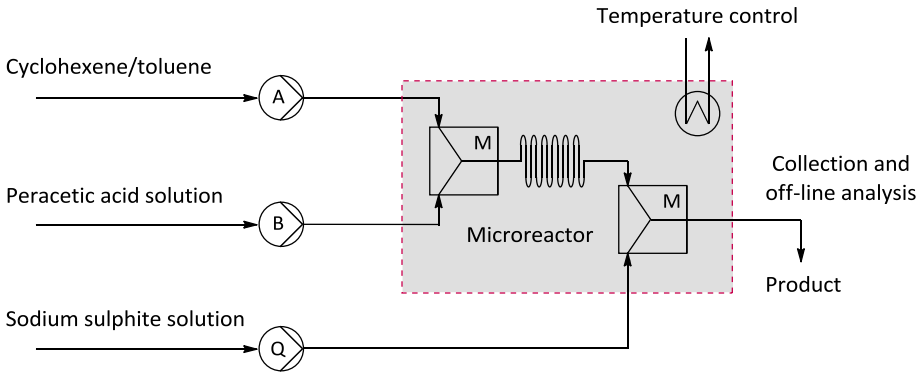

Figure 2: FlowStart setup for the Prilezhaev epoxidation

Chemicals

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

- peracetic acid (35% w/w solution in diluted acetic acid)
- cyclohexene
- sodium sulphite
- dichloromethane
- toluene (used as internal standard)

Stock solutions

A. Cyclohexene/toluene (5:1 vol/vol; corresponding to 8.3 M)
B. Peracetic acid (35% w/w solution in diluted acetic acid; corresponding to 5.4 M)
Q. Sodium sulphite 1.0 M in water (corresponding to 1.0 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 (toluene) is done using general methodology. For a quick calibration, make 4 samples with a fixed toluene 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.

Do **NOT USE ACETONE** while working with peracetic acid (or any other peroxides), as this can lead to the formation of dangerously explosive compounds.

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 Prilezhaev epoxidation 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)	0.5 min	5.0 min
peracetic acid/cyclohexene molar excess ratio ($ME_{B/A}$)	0.5	3.0
Temperature (T)	20°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 200 µL, all samples are collected in a GC vial containing 400 µL dichloromethane. Quenching molar excess ratio ($ME_{Q/B}$) is fixed to 1.0. The used setup can be seen in Figure 2.

Prilezhaev epoxidation 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 Prilezhaev epoxidation 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 Prilezhaev epoxidation in flow.

During the experiments, be sure to **collect all your waste in a separate container**. While cleaning up, destroy all your unreacted peracetic acid in the waste container by adding an excess sodium sulphite solution to the waste solution.
This means that if you use a certain amount of solution B during the experiments, add at least 10 times as much solution C to the waste solution before disposal.

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 Prilezhaev epoxidation, and show the essential (sequential) steps from cyclohexene and peracetic acid to diol.**

3. **Q: What advantages in performing the Prilezhaev epoxidation in continuous flow can you think of? Also, can you think of any disadvantages?**

4. **Q: Because the cyclohexene/toluene solution does not mix with the peracetic acid solution, the Prilezhaev epoxidation reaction is carried out in a two-phase system (comparable to an 'oil-in-water' system). You can observe this in the microreactor by the formation of so-called *plugs*. The actual reaction takes place at the *interface* (area of contact) of these plugs. Can you think of advantages to this plug-flow reaction? Also, what are the disadvantages? What possible solutions could circumvent this two-phase system, and what are its (dis)advantages?**