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.

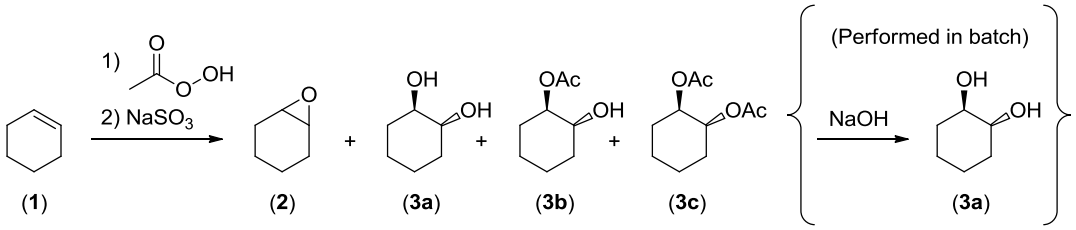

Figure 1: Prilezhaev epoxidation scheme

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)

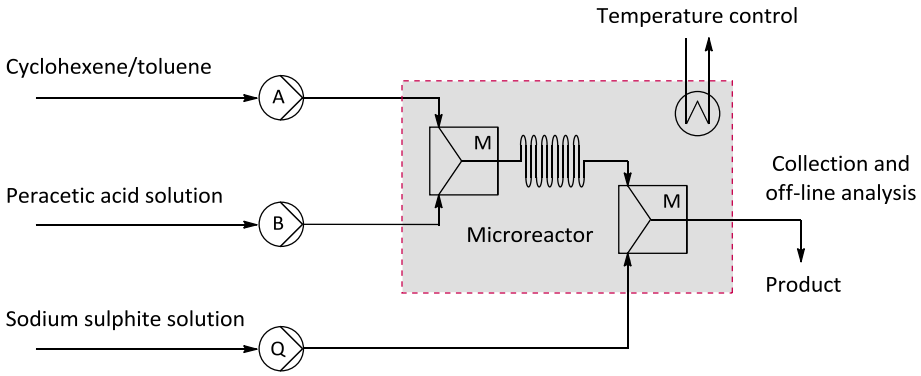

Figure 2: FlowStart setup for the Prilezhaev epoxidation

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.

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 Prilezhaev epoxidation at fixed parameters – a reaction time (t_R) of 2.0 min, a temperature of 60°C and an peracetic acid molar excess ratio ($ME_{B/A}$) of 1.1. The Q/B molar excess ratio ($ME_{Q/B}$) is set to a fixed value of 1.0. The target volume of solution A to be collected is 200 µL, all samples are collected in a GC vial containing 400 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

- Prepare solutions A, B and Q
- Fill the three syringes with solutions A, B and Q
- 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 5 minutes
- Collect your sample for the calculated time
- Analyse your sample using gas chromatography and calculate substrate conversion 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

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

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.

Preparative scale experiment

The reaction mixture from the previous microreactor experiment can also be used to synthesise the diol by hydrolysis with sodium hydroxide. To do this, collect a certain amount of reaction mixture (e.g. 5 mL) and calculate the starting amount (in mmol) of cyclohexene present in this mixture. Remove all excess water, acetic acid, cyclohexene and toluene by rotary evaporation. Add 2 equivalents of sodium hydroxide as a 5 M solution and heat to 60°C while stirring for 45 minutes. After cooling down, neutralise the solution to pH 7 with diluted aqueous HCl and evaporate to dryness by rotary evaporation. Extract the residue three times with ethyl acetate. Dry the combined organic fractions, filter and remove solvent by rotary evaporation to obtain the crude diol (determine yield). The pure diol can be obtained by recrystallisation from ethyl acetate. Determine melting point (lit. 100-104°C) and take an IR spectrum (see Appendix: IR spectrum of trans-1,2-cyclohexanediol).

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?**