

Aldol condensation in a continuous flow microreactor

Background

The aldol condensation of benzaldehyde and acetone is a textbook example of an exothermic, spontaneous reaction which is often performed during practical courses at universities and high schools. Due to its exothermic character, the reaction vessel is traditionally cooled in an ice bath, with controlled reagent addition to avoid the formation of side products and evaporation of acetone. The product dibenzylideneacetone is used as a UV blocker and as a ligand in organometallic chemistry.

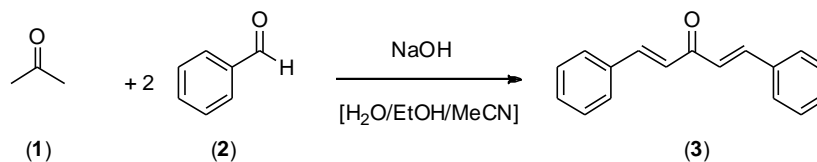


Figure 1: Aldol condensation scheme

Using continuous flow chemistry, aldol condensations are suitable for large-scale, preparative synthesis of unsaturated compounds. In continuous flow, a ketone (1) and an aldehyde (2) are introduced into the microreactor, where they react to form the corresponding aldol condensation product (3).

Setup and method

Material

- FlowStart B-200
- B-230 Pump Module
- B-242 Inlet Module
- 3x plastic 10 mL syringe
- Basic Microreactor (internal volume $V_{\mu R} = 100 \mu\text{L}$)

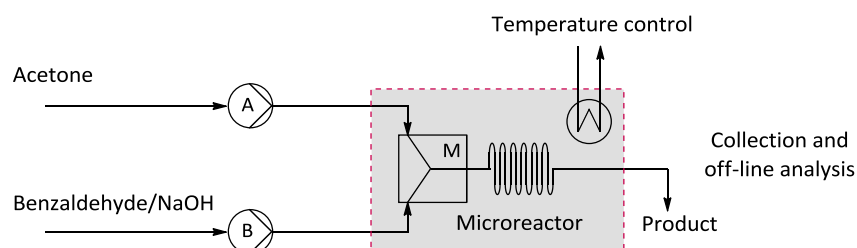


Figure 2: FlowStart setup for the Aldol condensation

Chemicals

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

- benzaldehyde
- sodium hydroxide
- acetone
- acetic acid
- acetonitrile/ethanol/water

Stock solutions

- A. 128 μL acetone (1.75 mmol) dissolved to a total volume of to 10 mL with acetonitrile/ethanol/water (1:1:1) (corresponding to 0.18 M)
- B. 140 mg sodium hydroxide (3.5 mmol) and 357 μL (3.5 mmol) benzaldehyde dissolved to a total volume of to 10 mL with acetonitrile/ethanol/water (1:1:1) (corresponding to 0.35 M)
- Q. 3.2 mL acetic acid diluted to a total volume of 100 mL with acetonitrile/ethanol/water (1:1:1) (corresponding to 0.56 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 UV-vis. Calibration of the product is done using general methodology. For a quick calibration, make 4 samples with a varying compound concentration. Analyse these samples and 1) setup a calibration curve of absorption against concentration and/or 2) determine the 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 Aldol condensation 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)	1.0 min	15 min
benzaldehyde/sodium hydroxide/acetone molar excess ratio ($ME_{B/A}$)	0.5	4.0
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 2.0 μL , all samples are collected in a vial containing 10.0 mL of solution Q. The vial must be wrapped in aluminium foil to prevent degradation. The used setup can be seen in Figure 2.

Aldol condensation 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 ($t_{\text{stab}} = 2 \cdot t_{\text{R}}$).
- 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 Aldol condensation in flow.

Analysis:

- Measure the samples using UV-vis, 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 Aldol condensation 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 Aldol condensation, and show the essential (sequential) steps from acetone and benzaldehyde to the aldol condensation product dibenzalacetone.**
3. **Q: What advantages in performing the Aldol condensation in continuous flow can you think of? Also, can you think of any disadvantages?**