Wittig reaction in a continuous flow microreactor

Background

A convenient and selective way of forming a carbon-carbon double bond is through the Wittig reaction and its modifications. Although easily performed in batch, the Wittig reaction could be incorporated in a total synthesis using continuous flow. The latter has the added advantage of handling all toxic and corrosive reagents inside a closed system.

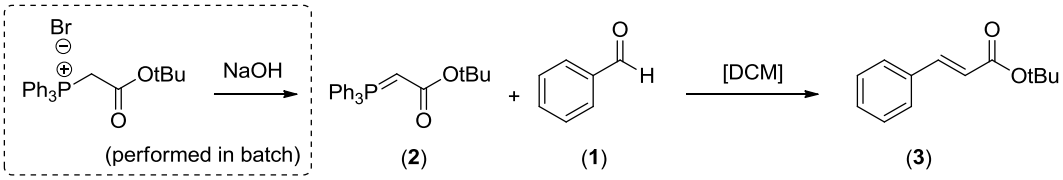

Figure 1: Wittig reaction scheme

The phosphonium ylide reagent is prepared in batch, by deprotonation of the corresponding Wittig salt. In continuous flow, an aldehyde (1) and a phosphonium ylide (2) are introduced into the microreactor, where they react to form the corresponding unsaturated Wittig product (3). The Wittig reaction is an example of a very selective reaction, producing no side products. However, the formed double bond can take two configurations: the *cis* (Z) and the *trans* (E) form. The latter is shown in Figure 1.

Setup and method

Material

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

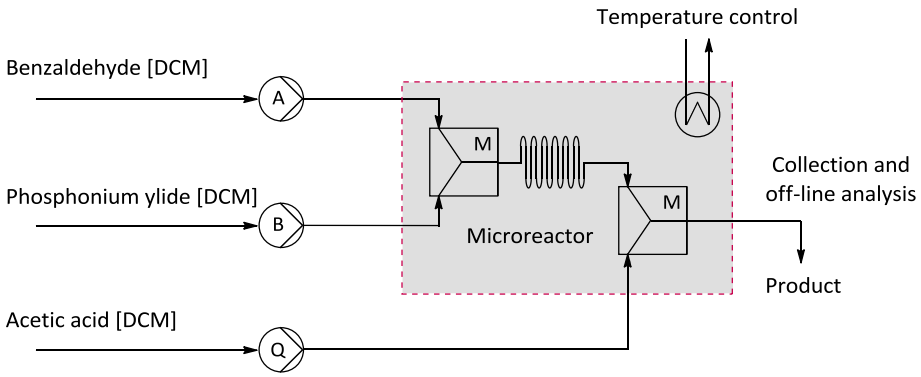

Figure 2: FlowStart setup for the Wittig reaction

Chemicals

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

- tert-Butoxycarbonylmethyl phosphonium bromide (Wittig salt)
- benzaldehyde

- sodium hydroxide (0.2 M solution)
- acetic acid
- dichloromethane (DCM)
- anisole (used as internal standard)

Stock solutions

A. Benzaldehyde (102 µL, 1.00 mmol) and anisole (109 µL, 1.00 mmol) dissolved to a total volume of 10 mL with dichloromethane (corresponding to 0.1 M)

B. Stir 457 mg (1.00 mmol) of the Wittig salt (in 5 mL dichloromethane) with 7.5 mL 0.2 M NaOH for 10 minutes. Separate layers, dry, filter and fill up to a total volume of 10 mL with dichloromethane (corresponding to 0.1 M)

Q. Acetic acid (1.73 mL, 30.0 mmol) dissolved to a total volume of 10 mL with dichloromethane (corresponding to 3.0 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 (anisole) is done using general methodology. For a quick calibration, make 4 samples with a fixed anisole 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 Wittig reaction 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
phosphonium ylide/benzaldehyde molar excess ratio ($ME_{B/A}$)	1.0	8.0
Temperature (T)	0°C	30°C

The stabilisation time for this reaction is two times the reaction time. The target volume of solution A to be collected is 20 µL, all samples are collected in a GC vial containing 500 µL dichloromethane. Quenching molar excess ratio ($ME_{Q/B}$) is fixed to 20. The used setup can be seen in Figure 2.

Wittig reaction 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 Wittig reaction 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 Wittig reaction 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 Wittig reaction, and show the essential (sequential) steps from benzaldehyde and tert-Butoxycarbonylmethyl phosphonium bromide (phosphonium ylide) to Wittig product.**

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