Paal-Knorr reaction in a continuous flow microreactor

Background

The synthesis of pyrroles through the Paal-Knorr reaction is a useful reaction in organic chemistry, as the starting materials react almost instantaneously without formation of byproducts. Traditionally, this reaction is very difficult to control due to its fast reaction rate and exothermic character. In large-scale batch synthesis, the Paal-Knorr reaction is therefore replaced by other methods to synthesise pyrroles.

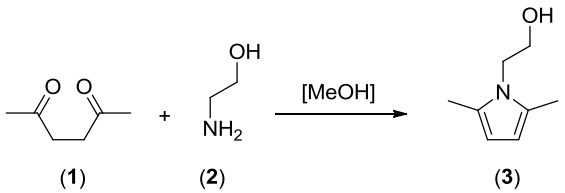

Figure 1: Paal-Knorr reaction scheme

Using continuous flow chemistry, the Paal-Knorr reaction is suitable for large-scale, preparative synthesis of (substituted) pyrroles. The latter has the added advantage of handling all toxic and corrosive reagents inside a closed system. In continuous flow, a 1,4-diketone (**1**) and a primary amine (**2**) are introduced into the microreactor, where they react to form the corresponding pyrrole (**3**).

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)

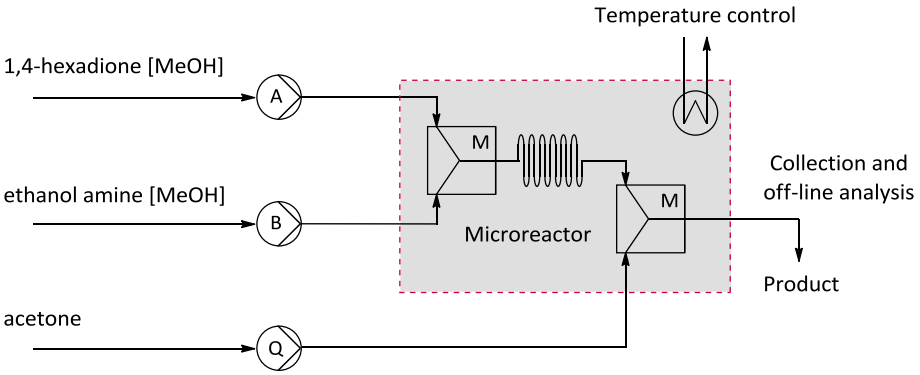

Figure 2: FlowStart setup for the Paal-Knorr reaction

Chemicals

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

- 2,5-Hexadione (also called: acetonyl acetone)
- Ethanol amine
- Methanol
- Acetone
- 2-Bromotoluene (used as internal standard)

Stock solutions

- **A.** 1,4-Hexadione/2-bromotoluene/methanol (9:1:10 v/v; corresponding to 3.84 M)
- **B.** Ethanol amine/methanol (1:1 v/v; corresponding to 8.28 M)
- **Q.** Acetone (corresponding to 13.64 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 (2-bromotoluene) is done using general methodology. For a quick calibration, make 4 samples with a fixed 2-bromotoluene concentration and a varying substrate 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 Paal-Knorr reaction at fixed parameters – a reaction time (t_R) of 1.7 min, a temperature of 20°C and an ethanol amine molar excess ratio ($ME_{B/A}$) of 5.0. The Q/B molar excess ratio ($ME_{Q/B}$) is set to a fixed value of 5.0. The target volume of solution A to be collected is 100 µL and all samples are collected in a GC vial containing 800 µL acetone. 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 and B
- Fill the three plastic 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 the GC and calculate diketone 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

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 pyrrole product in a preparative manner. To do this, collect a certain amount of reaction mixture (e.g. 5 mL) and calculate the starting amount (in mmol) of the diketone present in this mixture. Remove all excess methanol by rotary evaporation and add 10 volumes of diethyl ether. Wash this mixture with 1 M HCl and brine, dry the ether layer, filter and remove solvent by rotary evaporation to obtain the crude pyrrole (determine yield). The pure pyrrole can be obtained by recrystallisation from petroleum ether. Determine melting point (lit. 52-53°C) and take an IR spectrum (no reference

available; try to interpret the fingerprint area) or a proton NMR (lit. ^{1}H-NMR(300 MHz, $CDCl_3$) δ (ppm): 5.82 (s, 2H), 3.94 (t, 2H, J=6 Hz), 3.78 (t, 2H, J=6 Hz), 2.28 (s, 6H)). Purity can also be assessed by GC.

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 pyrrole product.**
    b. **Find the safety aspects (R/S values) of the used chemicals.**

2. **Q: Find the reaction mechanism for the Paal-Knorr reaction, and show the essential (sequential) steps from diketone and amine to the pyrrole product. (Note: there is still some debate on what the actual mechanism is, so multiple answers are plausible.)**

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