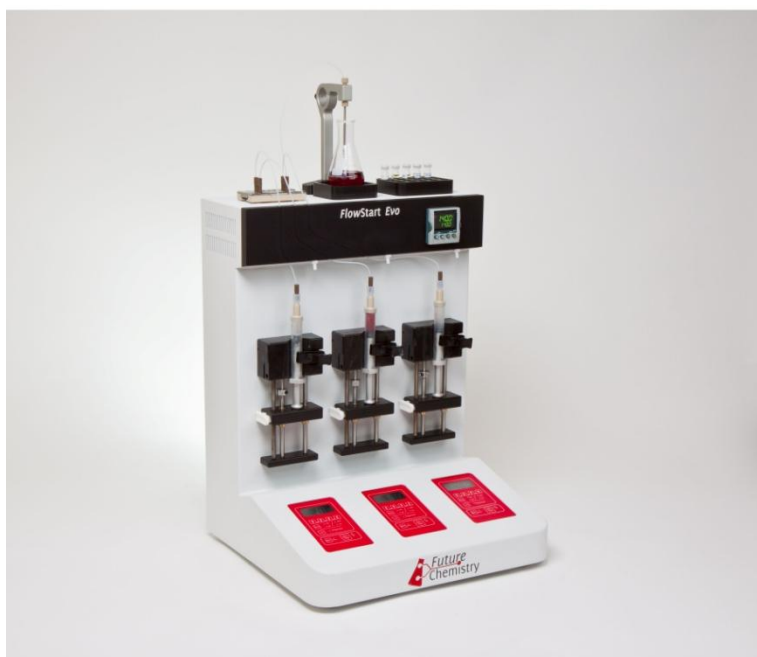# Application Note 8.4

Aldol condensation: synthesis of dibenzalacetone

The aldol condensation of benzaldehyde and acetone is a classical example of a spontaneous, exothermic reaction. To avoid controlled reagent addition and cooling, the reaction was successfully translated from batch to continuous flow in the *Flow*Start *Evo* microreactor platform, providing an alternative to the conventional batch process running at much higher temperatures than the batch reaction.

Introduction

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 dibenzalacetone is used as a UV blocker and as a ligand in organometallic chemistry.
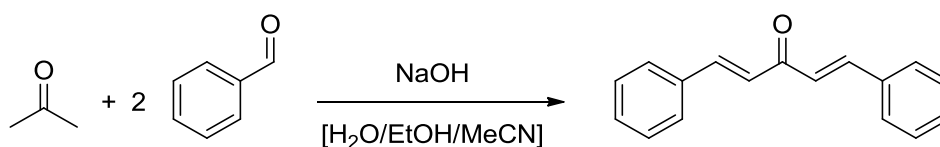

Figure 1: Aldol condensation of benzaldehyde and acetone to dibenzalacetone

To avoid the use of cooling and controlled reagent addition, FutureChemistry has translated this reaction from a batch process to a continuous flow process. FutureChemistry's typical three-tier approach led to a protocol which can be adapted to any viable aldol condensation:

1) Translation of batch process to continuous flow process:
    a) Stock solutions approach, yielding a homogeneous reaction mixture.
    b) Quenching solution to follow the reaction in time.
    c) Flow markers approach to accurately assess reaction parameters.
2) Automated reaction optimisation.
3) Out scaling to preparative synthesis.

This *application note* describes the translation of the batch process to the continuous flow process using the *Flow*Start *Evo* B-401.

Batch to flow conversion

In contrast to batch chemistry, reactions in continuous flow are conducted from stock solutions. These solutions should remain inactive after preparation, but react when combined. In the dibenzalacetone synthesis, solution A contains the acetone, solution B contains the benzaldehyde and sodium hydroxide catalyst, and solution Q contains the acetic acid. The used flow setup is depicted in Figure 2.
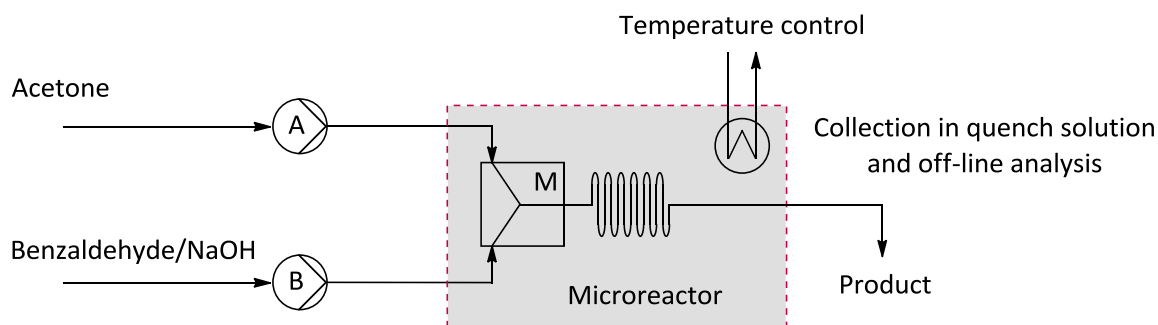

Figure 2: *Flow*Start *Evo* **setup**

To stop the reaction at a certain point in time a quenching agent is needed, which reacts with the reagent many times faster than the reaction itself. In the dibenzalacetone synthesis, acetic acid is used to neutralise the used sodium hydroxide.
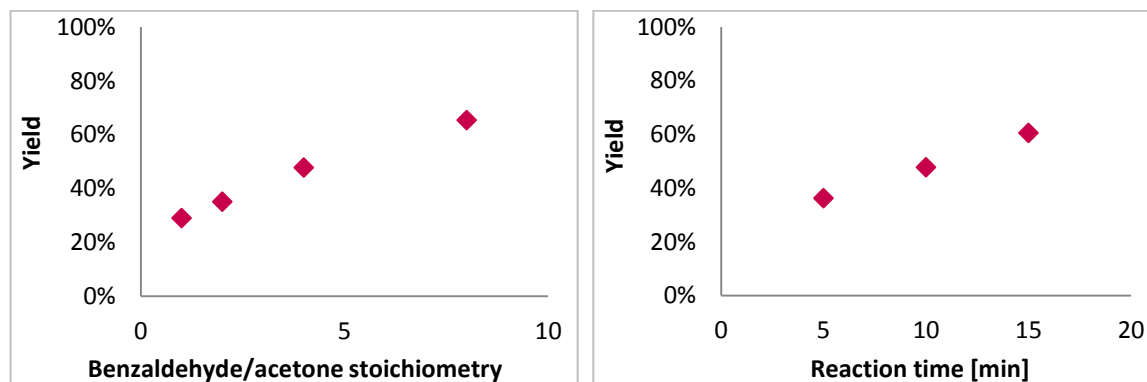

Figure 3: Results of the aldol condensation (1)
Left: Dibenzalacetone yield *vs.* benzaldehyde/acetone stoichiometry (temperature 60°C, reaction time 10 min)
Right: Dibenzalacetone yield *vs.* reaction time (temperature 60°C, benzaldehyde/acetone stoichiometry 4.0)

In the *Flow*Start *Evo* experiments, temperature, TFAA/alcohol stoichiometry and reaction time were varied. *Basic reaction parameters* were defined as having a temperature of 60°C, reaction time of 10 min and benzaldehyde/acetone stoichiometry of 4.0, around which all univariate screening experiments were performed. The boiling point of acetone limited the use of higher temperatures.
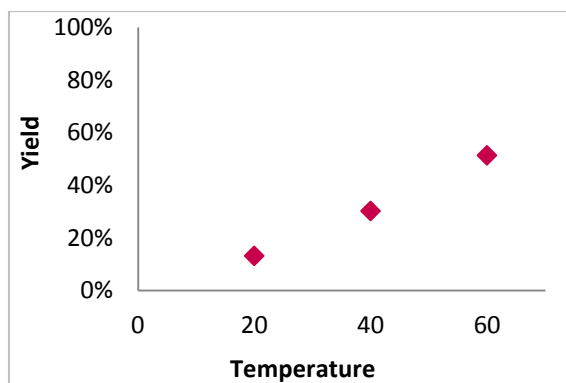
Figure 4: Results of the aldol condensation (2)
Dibenzalacetone yield *vs.* temperature (reaction time 10 min, benzaldehyde/acetone stoichiometry 4.0)

The univariate screening of the aldol condensation of benzaldehyde and acetone showed a linear increase of yield with all three parameters. An optimum was therefore not found, but could probably be obtained by using more equivalents of benzaldehyde or a longer reaction time. With the above parameter values, yields up to 70% were observed, and the aldol condensation of benzaldehyde and acetone was successfully converted from batch to flow.

The synthesis of dibenzalacetone in a continuous flow microreactor can be regarded a modern alternative to the procedure used in chemistry education. Advantages and disadvantages of both methods can be compared, to provide insight on chemical engineering-based considerations.

Method

All experiments were conducted in a standard FutureChemistry B-401 *Flow*Start *Evo* setup, using the Basic Microreactor with internal volume of 100 µL.

Solution A (0.18 M): Acetone (125 µL, 1.75 mmol) dissolved to a total volume of 10 mL with the used solvent mixture

Solution B (0.34 M): Sodium hydroxide (133 mg, 3.33 mmol) and benzaldehyde (350 µL, 3.44 mmol) dissolved to a total volume of 10 mL with the used solvent mixture

Solution Q (0.56 M): Acetic acid (3.2 mL, 55.9 mmol) dissolved to a total volume of 100 mL with the used solvent mixture

Solvent mixture Water/ethanol/acetonitrile 1:1:1

Two plastic 10 mL syringes were loaded with solutions A and B respectively. For each experiment, the desired flow rates were calculated according to the following equations:

Total flow = microreactor volume / reaction time

Flow A = total flow / (1 + Benzaldehyde/acetone stoichiometry / 1.89)

Flow B = Flow A * (Benzaldehyde/acetone stoichiometry / 1.89)

For every experiment, a target volume of solution A of 2.0 µL was collected in a vial containing 10 mL solution Q. Analysis was performed on a Varian Cary 50 UV-Vis spectrophotometer, using a quartz cuvette, at an absorption wavelength of 331 nm. UV-Vis absorption of 1.0 AU corresponded roughly with a yield of 100%, using the sample dilution described above.