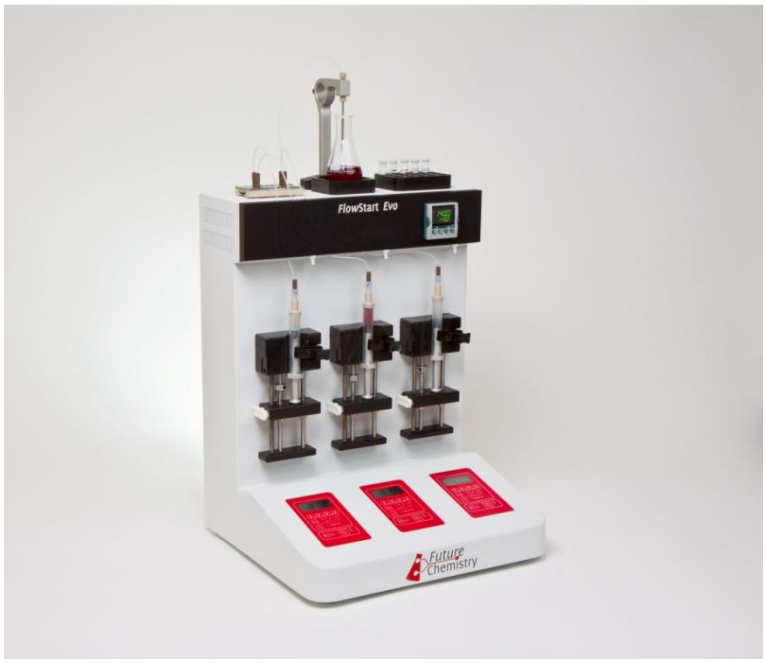
# Application Note 12.4

## *Methylation with diazomethane*




Diazomethane reactions are quite eagerly performed by chemists on a small scale, as the reaction tends to be highly selectively, giving very pure reaction mixtures in high yields. On larger scales, however, the reaction is mostly avoided on safety concerns. The methylation with diazomethane was successfully translated from batch to continuous flow in the *Flow*Start *Evo* microreactor platform, providing a safer alternative to the conventional batch process.

Future Chemistry

## Introduction

Reactions employing diazomethane as a methylating agent are very useful in organic synthesis, due to their high selectivity and yields. However, preparing diazomethane from one of the available precursor compounds requires much care, since it is a highly reactive species which can spontaneously explode on contact with sharp edges. Also, the reagent is very toxic, requiring good ventilation and safety measures to handle any unwanted liberation of diazomethane.

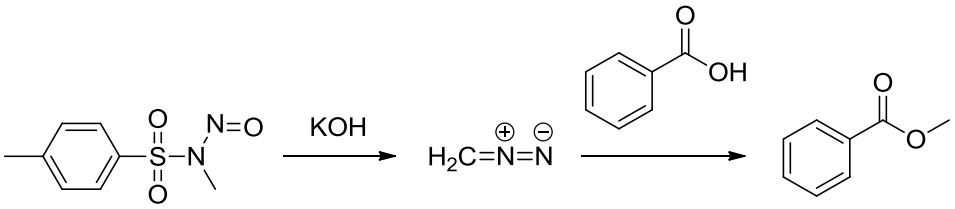



**Figure 1: Methylation of benzoic acid with diazomethane**

In general, diazomethane chemistry is dangerous. To be able to handle this explosive and toxic compound in a closed system, 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 substrate:

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.
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 benzoic acid methylation, solution A contains the diazomethane precursor Diazald, solution B contains potassium hydroxide and solution Q contains benzoic acid. The used flow setup is depicted in Figure 2.

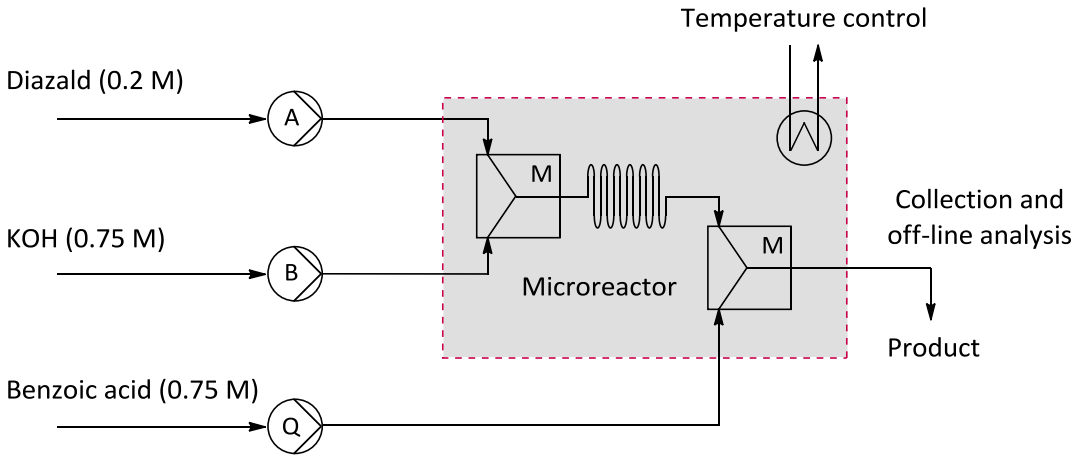



**Figure 2: *Flow*Start *Evo* setup**

The first reaction in the microreactor is the formation of diazomethane, prepared by the treatment of Diazald with potassium hydroxide. The resulting solution of diazomethane is subsequently quenched with a solution of benzoic acid, thereby liberating a substantial amount of nitrogen gas. While stabilising, the outflow was collected in a flask containing acetic acid to quench any unreacted diazomethane.

In the *Flow*Start *Evo* experiments, temperature was fixed at ambient level. Reaction time of the diazomethane preparation was fixed at 56 sec; reaction time of the benzoic acid methylation was unknown due to gas liberation. Stoichiometry of potassium hydroxide to Diazald was fixed at 1.5; stoichiometry of benzoic acid to Diazald was fixed at 4.0. With the above parameter values, the yield of methyl benzoate with respect to Diazald was 27%, and the methylation of benzoic acid was successfully converted from batch to flow. The yield could probably be increased by increasing the residence time of the second reaction or by adding back pressure at the outflow channel.

## Method

All experiments were conducted in a standard FutureChemistry B-401 *Flow*Start *Evo* setup, using the Basic Quench Microreactor with internal volume of 92 µL. Benzoic acid was used as model substrate.

**Solution A** (0.2 M): 428 mg Diazald (N-methyl-N-nitroso-*p*-toluenesulfonamide, 2.0 mmol) dissolved to a total volume of 10 ml with carbitol

**Solution B** (0.75 M): 421 mg potassium hydroxide (7.5 mmol) dissolved to a total volume of 10 ml with *iso*-propanol

**Solution Q** (0.75 M): 916 mg benzoic acid (7.5 mmol) dissolved to a total volume of 10 ml with carbitol

Three glass 1.0 mL syringes were loaded with solutions A, B and Q respectively. For the experiment, the desired flow rates were fixed at:

Flow A = 71.4 µL/min

Flow B = 28.6 µL/min

Flow Q = 76.2 µL/min

All product mixtures were analysed with GC against an internal standard (added to solution Q), with retention times according to Table 1. Analysis was performed on a Shimadzu GC2010 using a Quadrex 007 1701 apolar column (L 15.0 m, ID 0.10 mm) and flame ionisation detector, using a temperature program (0-0.5 min 80°C, 0.5-7.3 min 80-250°C, 7.3-10 min 250°C) and 1.0 µL injection with split ratio 200.

**Table 1: GC analysis retention times**

| Compound | Function | Retention time [min] |
|---|---|---|
| **methyl benzoate** | product | 1.67 |