Application Note 1.4

Deprotection of p-methoxyphenyl (PMP) protected amines

Cleavage of the PMP amine protecting group – useful in the synthesis of enantiopure amines – has been shown to proceed under mild conditions by treatment with periodic acid, thereby avoiding laborious work-up procedures. The deprotection reaction was successfully translated from batch to continuous flow in the *Flow*Start *Evo* B-401 microreactor platform, providing a viable alternative to the conventional batch process.

Future Chemistry

Introduction

In the synthesis of enantiopure amines, *p*-methoxyphenyl (PMP) is often the most suitable protecting group, since the protection-deprotection sequence does not change the amine stereochemistry. Most literature procedures describe the deprotection with ceric ammonium nitrate, which involves column chromatography and produces highly toxic waste. Recently, a mild and efficient deprotection using periodic acid was reported[1] requiring only acid/base extraction, leading to an overall reduction of costs and a more environmentally benign process.
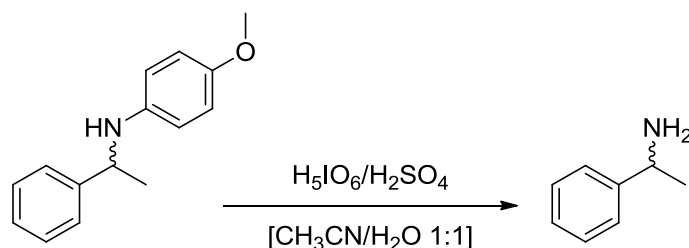

Figure 1: Deprotection of model substrate

Oxidative cleavage of the PMP group is a fast and exothermic reaction, which limits the feasibility of batch process up-scaling. FutureChemistry has therefore 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 PMP protected amine 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.
   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.

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[1] Verkade, J.M.M.; van Hemert, L.J.C.; Quaedflieg, P.J.L.M.; Alsters, P.L.; van Delft, F.L.; Rutjes, F.P.J.T. *Tetrahedron Lett.* **2006**, *47*, 8109.

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 PMP deprotection, solution A contains the protected amine and solution B contains the periodic acid reagent. The used flow setup is depicted in Figure 2.
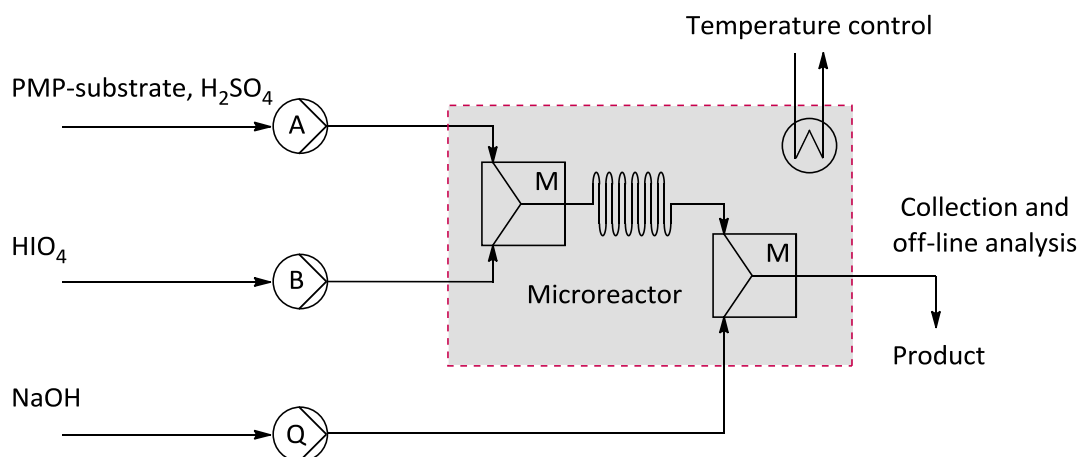

Figure 2: *Flow*Start *Evo* setup

To stop the reaction at a certain point in time a quenching agent is needed, which is many times faster than the reaction itself. In the PMP deprotection, sodium dithionite is used to remove all leftover periodic acid and sodium hydroxide is used to convert the formed benzoquinone to the less reactive hydroquinone.
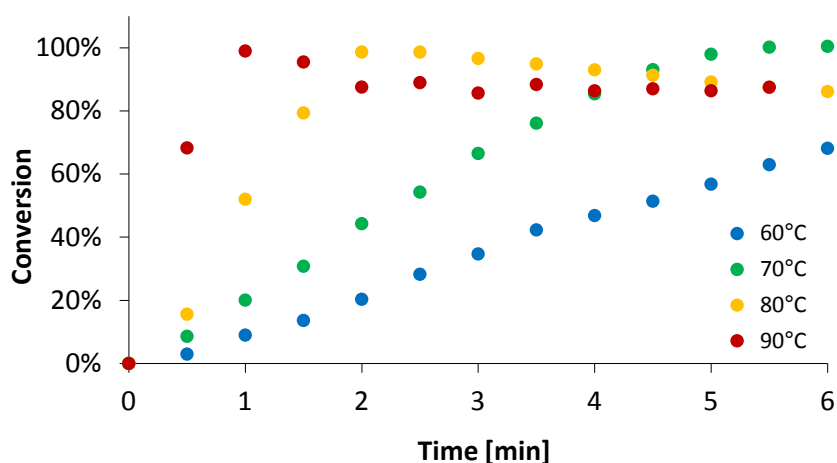

Figure 3: Substrate conversion at periodic acid stoichiometry of 1.0

In the *Flow*Start *Evo* experiments, temperature, stoichiometry and reaction time were varied. With a stoichiometry of 1.0, conversions from 0% to 100% were observed (Figure 3), and deprotection of the amine substrate was successfully converted from batch to flow.

Method

All experiments were conducted in a standard FutureChemistry *Flow*Start *Evo* B-401 setup. The microreactor used was custom made with dimensions: L 45 mm, W 15 mm, H 2.2 mm, channel dimensions: L 1325 mm, H 55 µm and internal volume of 7.02 µL.

Solution A (88.0 mM): PMP protected amine (200 mg, 0.880 mmol) and 880 µL 1 M sulfuric acid (0.880 mmol) dissolved to a total volume of 10 mL with CH_3CN/H_2O (1:1)

Solution B (88.0 mM): Periodic acid (201 mg, 0.880 mmol) dissolved to a total volume of 10 mL with CH_3CN/H_2O (1:1)

Solution Q: Sodium dithionite (391 mg, 2.24 mmol, 2.55 eq) dissolved to a total volume of 25 mL with CH_3CN/0.1 M NaOH (1:1)

Three glass 1.0 mL syringes were loaded with solutions A, B and Q 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 + periodic acid stoichiometry)

Flow B = Flow Q = Flow A * periodic acid stoichiometry

All product mixtures were analysed with HPLC, with retention times according to Table 1. Analysis was performed on a Shimadzu LC2010 using an Intersil ODS-3 column, eluting with CH_3CN/0.2 M phosphate buffer (pH 3) with a flow rate of 2.0 mL/min, detector wavelength 215 nm, using a gradient program (0-1 min 5%, 1-4 min 5-50%, 4-12 min 50%, 12-13 min 50-5%, 13-15 min 5% CH_3CN).

Table 1: HPLC analysis retention times

Compound	Function	Retention time [min]
deprotected amine	product	4.81
protected amine	substrate	13.6