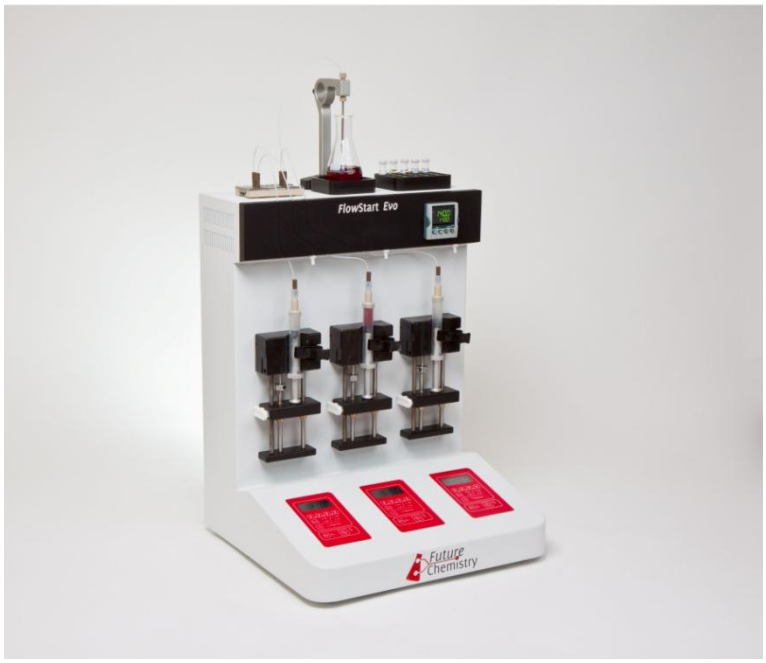
Application Note 3.4

Paal-Knorr pyrrole synthesis



The Paal-Knorr pyrrole synthesis is an age-old reaction, useful in the synthesis of pyrroles, thiophenes and furans. Since batch scale-up is limited due to the exothermic nature, the reaction was successfully translated from batch to continuous flow in the *Flow*Start *Evo* microreactor platform, providing a viable alternative to the conventional batch process.

Future Chemistry

Introduction

The Paal-Knorr pyrrole synthesis was first published in 1885 by Carl Paal and Ludwig Knorr. It is a spontaneous, moderately exothermic reaction, which can also be used in the synthesis of furans and thiophenes. Due to its exothermic nature, the reaction is of not much use in the chemical industry, since batch scale-up reaches its limits very quickly.

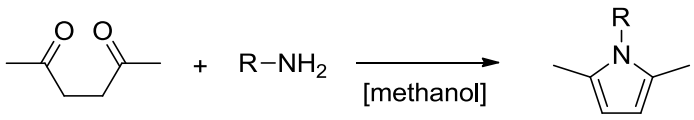


Figure 1: Paal-Knorr pyrrole synthesis. R = ethyl; 2-hydroxyethyl; 4-hydroxybutyl.

The Paal-Knorr pyrrole synthesis 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 amine/diketone substrate couple:

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 Paal-Knorr pyrrole synthesis, solution A contains the diketone and solution B contains the amine. The used flow setup is depicted in Figure 2. *Stoichiometry is defined as the amine to diketone ratio.*

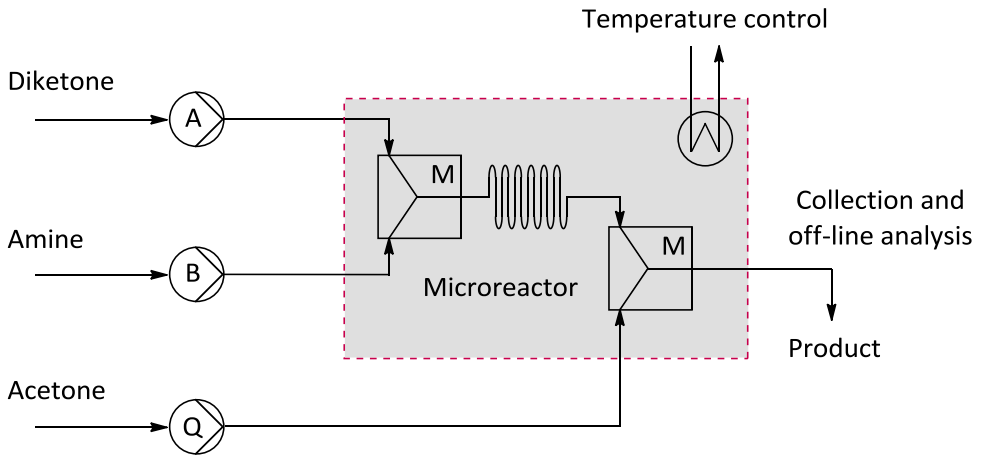


Figure 2: *Flow*Start *Evo* setup

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 pyrrole synthesis, acetone is used to deactivate all leftover amine by formation of the corresponding imine.

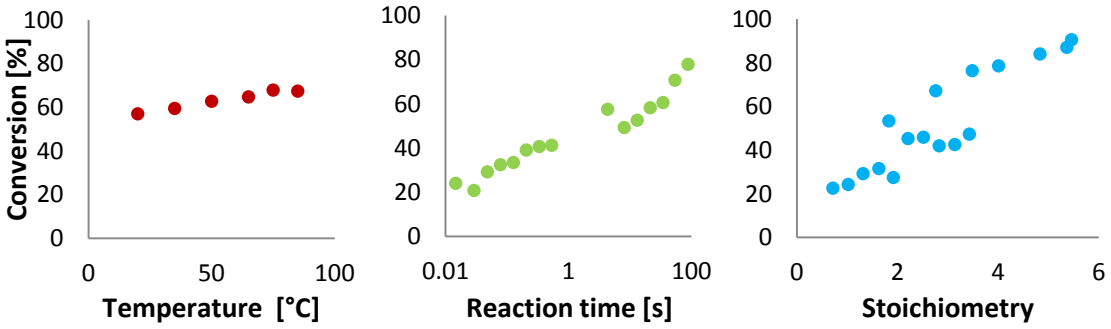


Figure 3: Substrate conversion univariate screening.
Fixed parameters: reaction time 12 s, stoichiometry 2.0, temperature 20°C.

In the *Flow*Start *Evo* experiments, temperature, amine stoichiometry and reaction time were varied. With the above parameter values, conversions from 20% to 90% were observed (Figure 3), and the Paal-Knorr synthesis 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 0.13 µL or 7.02 µL (depending on reaction time). Standard tests were performed using **2,5-hexadione** as diketone and **ethanolamine** as amine; ethylamine and *n*-butanol were found to be good alternative reagents.

Solution A: 2,5-Hexadione/methanol 1:1 (v/v)

Solution B: Ethanolamine/methanol 1:1 (v/v)

Solution Q: Acetone

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

Corrected stoichiometry = amine stoichiometry * (diketone concentration / amine concentration)

Flow A = total flow / (1 + corrected stoichiometry)

Flow B = Flow A * corrected stoichiometry

Flow Q = Flow B * (amine concentration / acetone 'concentration')

All product mixtures were analysed with GC, 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 (T 325°C, H_2 40 mL/min, Air 400 mL/min), using a temperature program (0-0.4 min 70°C, 0.4-1.2 min 70-90°C, 1.2-2.3 min 90-260°C) and 0.2 µL injection with split ratio 667.

Table 1: GC analysis retention times

Compound	Function	Retention time [min]
ethanolamine	reagent	0.68
2,5-hexadione	substrate	1.26
N-(2-hydroxyethyl)-2,5-dimethylpyrrole	product	1.99