Application Note 3.2

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 optimised in the *Flow*Screen microreactor platform. A reaction model was fitted using the optimisation data.

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.

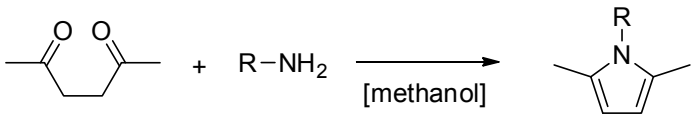

Figure 1: Paal-Knorr pyrrole synthesis. R = ethyl; 2-hydroxyethyl; 4-hydroxybutyl.

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.
2) Automated reaction optimisation:
   a) Univariate screening of reaction parameters.
   b) Selection of parameter range and optimisation points.
   c) Multivariate optimisation experiment.
   d) Analysis and modeling.
3) Out scaling to preparative synthesis.

This *application note* describes the optimisation of the continuous flow process using the *Flow*Screen C-300.

Reaction optimisation

In contrast to batch-wise optimisation of chemical reactions, optimisation in continuous flow offers some significant advantages. Firstly, each experiment can be carried out using material in the microgram or nanogram scale, thereby minimising waste and costs. Secondly, automated optimisation is a lot less time-consuming and more precisely controlled, especially when optimising fast reactions.

To obtain accurate concentration measurements of the reaction mixtures, a flow markers approach is used. To each stock solution, an internal standard is added. The collection fluid contains an external standard. The ratio of internal standards determines stoichiometry; the ratios between the internal and external standards determine the *actual* flow rates as opposed to the *set* flow rates. Accurate concentration measurements follow from calibration of the compounds onto the internal standards.

Table 1: Reaction parameter ranges

Parameter	Range
Temperature [°C]	20 to 85
Stoichiometry (reagent/substrate)	0.8 to 8.0
Reaction time [s]	0.1 to 100

To select a useful region for performing the optimisation experiment, three univariate optimisation experiments were conducted in the *Flow*Screen to show parameter influences. From this it followed that stoichiometry and reaction time had a pronounced effect on substrate conversion, with increasing conversion as parameter values increased, while temperature influence only played a minor role. The found parameter ranges are given in Table 1.

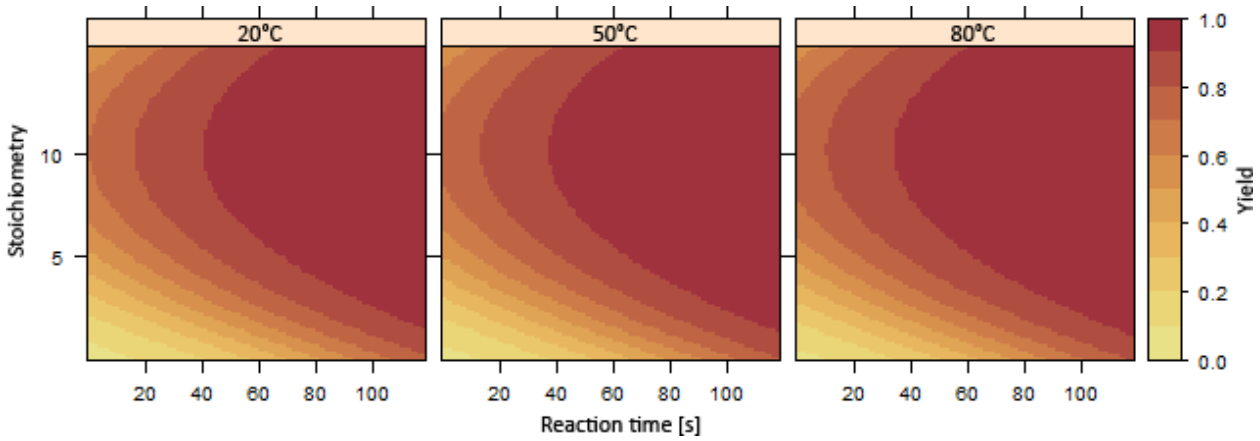

Figure 2: Reaction model fit. (Note: logarithmic time-scale.)

An optimisation experiment was set up with 87 points, spread out across the optimisation region. The experiment was prepared, uploaded to the *Flow*Screen controller and conducted in an automated fashion. Afterwards all samples were analysed, processed and an optimum was found at a **temperature of 20°C, amine stoichiometry of 5.0 and reaction time of 100 s**. Subsequently, all optimisation data was used to fit the reaction model, which is visualised in Figure 2.

Method

The used setup for the deprotection reaction is identical to the *Flow*Start setup (see: *Application note 3.1*). The used flow markers are given in Table 2.

Table 2: Used flow markers

Compound	Function	Used in
2-bromotoluene	internal standard	Solution A
dimethoxyethane	internal standard	Solution B
1-bromonaphthalene	external standard	Collection fluid

All experiments were conducted in a standard FutureChemistry *Flow*Screen C-300 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/2-bromonaphthalene/methanol 9:1:10 (v/v)

Solution B: Ethanolamine/dimethoxyethane/methanol 4:1:5 (v/v)

Solution Q: Acetone

Collection fluid: 1-bromonaphthalene (6.0 g, 29.0 mmol) filled up to 1.0 L with acetone

Three glass 1.0 mL syringes were loaded with solutions A, B and Q respectively. For each experiment, a target volume of 50 µL solution A was collected in a vial containing 1.0 mL collection fluid. Experiments were conducted in random order. Data modelling was done using FutureChemistry's *Flow*Fit software.

All product mixtures were analysed with GC, with retention times according to Table 3. 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 3: GC analysis retention times

Compound	Function	Retention time [min]
dimethoxyethane	internal standard	0.39
ethanolamine	reagent	0.68
2,5-hexadione	substrate	1.26
2-bromotoluene	internal standard	1.36
N-(2-hydroxyethyl)-2,5-dimethylpyrrole	product	1.99
1-bromonaphthalene	external standard	2.19