Flow chemistry for process development and optimisation

Royston, UK based Syrris Ltd has developed an automated and fully integrated micro flow system that allows synthesis and on-line analysis. Thousands of reactions with more than 40 different chemistries have been performed using the company's AFRICA system, demonstrating the many benefits of micro flow chemistry.

Interest in flow chemistry, and specifically micro flow chemistry, has shown a dramatic rise in the past five years. The benefits of flow and miniaturisation have been extensively demonstrated by a variety of academia and industry. Until recently however, this area of research has been limited to those prepared to develop their own apparatus. There has been a strong rise in interest in the AFRICA system developed by UK company Syrris Ltd due to the novel benefits offered, including:

Control: The system gives excellent, repeatable control of reaction conditions, ie time, temperature, equivalents of reagents and mixing, and allows exothermic reactions to be performed without the need for cryogenics.

Increased reaction rate: By easily pressurising the system (eg to 300psi), reactions can be superheated to give reaction rates hundreds of times faster than in reflux. This gives microwave-like rate enhancement without the problems associated with scaling up microwave-based reactions.

Integrated synthesis and analysis: Reactions flow immediately from the reactor to the HPLC via a sampler and dilutor that takes a 5µl sample from the reaction mixture and dilutes it before flowing it onto the HPLC.

Automation: The reaction and analysis conditions are simply defined in the software and the system runs a variety of reaction conditions unattended.

Efficiency: The system operates with low raw materials consumption when working in method development mode eg 100µl per reaction.

Range of use: The system can be used for synthesis, reaction optimisation or for libraries, operating from 1mg per experiment to 200g per day. For example to optimise a reaction, a number of reactions can be performed using a structured exploration of parameters such as time, temperature and stoichiometry. The parameters to be used can be generated by Design of Experiment (DoE) software and imported into the AFRICA software. Once optimised, the preferred conditions can be used to generate larger amounts of material or to run a library.

Scalability: AFRICA gives good process scalability from discovery through to development and ultimately to manufacture.

Closed loop: The system has potential for closed loop reaction optimisation in the medium term and closed loop drug discovery in the long term.

Process development and optimisation

Process chemists have a need to perform and analyse reactions in a high-quality, controlled and repeatable fashion. In the AFRICA system, shown schematically in Fig 1, due to the small diameters of the flow reactors, mixing occurs by diffusion across very short distances (typically ~100µm), giving excellent reproducibility rather than chaotic, turbulent mixing found in batch reactors. Due to the large surface area to volume ratios found in microreactors, heat from exothermic reactions can be removed, or heat applied to a reaction extremely rapidly, giving excellent temperature control. By flowing the product of one reaction into another reactor, multi-step synthesis can be performed with exact timing of reagent or quench addition as a continual process. All of this, coupled with fully integrated, on-line HPLC analysis, allows the process chemist to carry out high-quality synthesis and analysis.

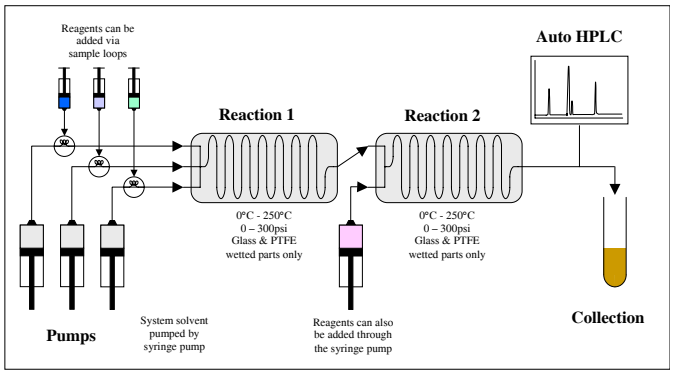

Fig 1. Schematic illustration of the operation of the AFRICA flow reactor system developed by Syrris Ltd.

Reaction optimisation (1): The AFRICA system is ideally suited to automated reaction optimisation. Parameters such as time, temperature, equivalents of reagents and order of addition can be easily investigated. To demonstrate this a Passerini 3CR reaction in the literature[1] that was part of a library of compounds was optimised (Fig 2). The objective was to optimise the procedure to reach the highest yield of desired product with a maximum of 1 hour reaction time.

The literature[1] reaction conditions were 60 hrs at room temperature with a 1:2:1 ratio of acid:aldehyde:isonitrile. These

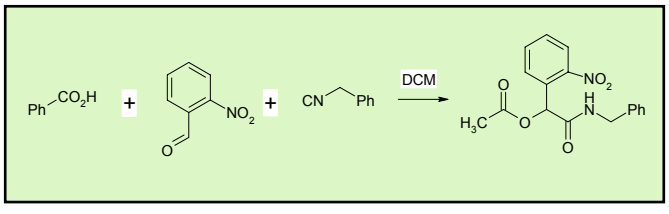

Fig 2. The Passerini 3CR reaction illustrated was used in a study to demonstrate the automated reaction optimisation capability of the AFRICA flow reactor system.

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conditions were repeated at Syrris and generated a yield of 62% (determined by HPLC with a calibrated internal standard). A design of experiment consisting of 16 reactions was carried out to investigate the following four variables within the specified ranges:

Time: 15, 30 and 60 mins - Due to the unacceptably long time for the literature batch reaction, a maximum of 1 hour was decided upon for the flow reaction.

Temperature: 80ºC and 100ºC - To reduce the reaction time to below 1 hour, the minimum temperature chosen was 80ºC. The maximum of 100ºC was defined due to the capacity of the AFRICA system with dichloromethane (DCM). Note that the temperatures are significantly greater than the atmospheric boiling point of DCM, which is 40ºC.

Equivalent ratios: Equivalents of isonitrile (vs acid): 0.7, 1 and 1.3 equivalents, and equivalents of aldehyde (vs acid): 0.7, 1 and 1.3 equivalents - it was decided that a very large equivalent of any reagent would not be investigated due to the poor efficiency of using large excesses.

By running these conditions automatically in AFRICA, the optimum conditions within the boundaries set were found to be 60 mins, 80ºC, 1:0.7:1.3 acid:aldehyde:isonitrile, giving a yield of 91%. The reaction was therefore optimised from a batch reaction of 62% (60 hour reaction) to 91% yield (1 hour reaction) using the AFRICA system and a DoE approach.

Reaction optimisation (2): In the following example, the AFRICA system was used to investigate the ratio of mono:di alkylation of benzylamine with benzyl bromide (Fig 3).

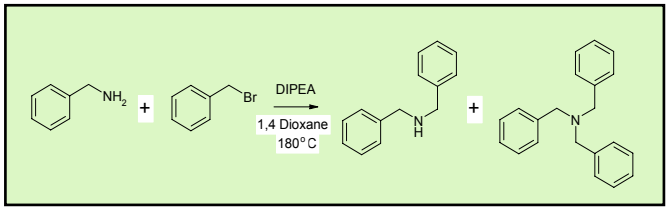

Fig 3. In a second reaction optimisation experiment, alkylation of benzylamine with benzyl bromide was investigated.

Initial studies of time and temperature demonstrated that the reaction could be superheated to 180ºC to dramatically increase the reaction rate (note that this is not even possible in a microwave due to the lack of dipole moment in dioxane). This allowed a variety of reagent equivalents to be investigated in quick succession. From the results, it was seen that it was possible to reduce the quantity of dialkylated product by increasing the ratio of benzylamine to benzyl bromide.

Scaling up

The AFRICA system can not only perform reactions on a small scale for optimisation but, once the preferred conditions are known, the flow rate can be increased to produce hundreds of grams of product. Due to reactor volumes of up to 16ml and flow rates of 2.5 ml/min per input, reaction scales in the order of litres can be synthesised overnight.

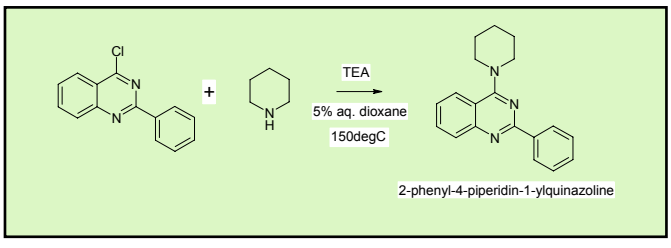

Fig 4. The nucleophilic aromatic substitution reaction illustrated was easily scaled up using the AFRICA system.

Combining automated flow synthesis and analysis, the AFRICA system is ideally suited to reaction optimisation.

The nucleophilic aromatic substitution reaction shown in Fig 4 was performed using the AFRICA system to synthesise 50g of product in 24hrs. The reaction was performed at 150ºC despite the atmospheric boiling point of the solvent being 100ºC by using pressurisation and, therefore, the superheating capability.

Prospects for the system

The AFRICA system already has the ability to vary reaction conditions and analyse each reaction quantitatively in an automated fashion. The next step for Syrris is to 'close the loop' and have the software select which reactions to investigate next, based on the results of previous experiments. With Closed Loop Reaction Optimisation, the user would be able to select the objectives of the optimisation and select the preferred optimisation algorithm. The result would be a system that would be able to optimise a reaction from start to finish and even email the user the preferred conditions when met.

In the past, drug discovery was performed in a slow, serial fashion. Syrris envisages a future where compounds will rapidly flow out of the reactor, through purification/solvent exchange and into the biological assay. Real-time SAR coupled with computational chemistry will allow software to select the next target in the library to be synthesised. This fast serial approach will give much greater efficiency and speed. sp²

REFERENCE

1. *Colour Encoded Parallel Synthesis,* Lorenzo Williams, The 3rd International Electronic Conference on Synthetic Organic Chemistry.

FURTHER INFORMATION

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