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Master of Science HES-SO in Life Sciences

Continuous synthesis of CS-Amide

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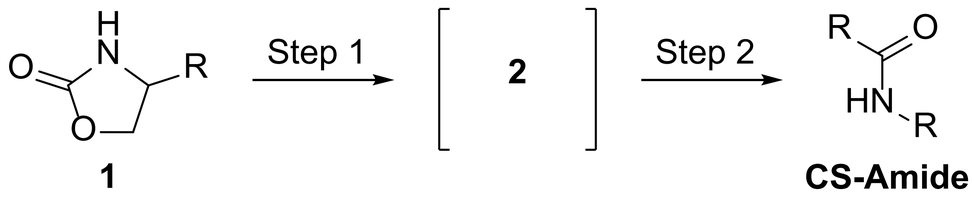
DESCRIPTION

Continuous chemistry offers many advantages such as increased safety, better productivity, lower product costs, improved process repeatability, higher yield, conversion and selectivity. Continuous chemistry also allows working under high pressures and/or temperatures, which would be technically unfeasible in batch mode. Highly exothermic reactions can also be safely operated in continuous mode as very good heat exchange is obtained, thus limiting heat accumulation. Residence times are generally shorter in continuous mode. Online analysis also allows the effect of variables on reaction performance to be known immediately. All these points show that it can be advantageous to transform a batch process into a continuous process.

Syngenta has developed a synthesis, purification and isolation of an amide from an oxazolidine (**1**) in batch mode. The reaction mechanism involves the formation of an intermediate (**2**) that is not isolated as it is unstable and is directly converted in-situ to the CS-Amide.



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OBJECTIVES

The aim of this work was to develop and optimize the continuous mode synthesis of CS-Amide, with three objectives.

- Develop a method for on-line monitoring the chemical conversion of the first step
- Develop and optimize the yield of step 1 in continuous mode by using design of experiment (DOE).
- Develop and optimize the yield of step 2 in continuous mode by using design of experiment (DOE).

Four main challenges related to the synthesis procedure had to be overcome in order to achieve the different objectives mentioned above :

1. The starting oxazolidine is a solid that must be pumped as a suspension.
2. The formation of the intermediate results in the formation of one equivalent of CO_2.
3. The second synthesis step takes place in a biphasic system (organic - aqueous).
4. The final reaction mixture may precipitate if the temperature is significantly reduced.

RESULTS

Continuous synthesis of (2) and CS-Amide

Better yield and much better Space Time Yield of (2) are obtained with the continuous setup (only step 1) compared to batch mode (Figure 1, Table 1).

The continuous synthesis in a PFR followed by a CSTR in series (Figure 1) gives the CS-Amide with a better yield and much better Space Time Yield (Table 1). The increase in Space Time Yield is mainly due to the shorter residence time.

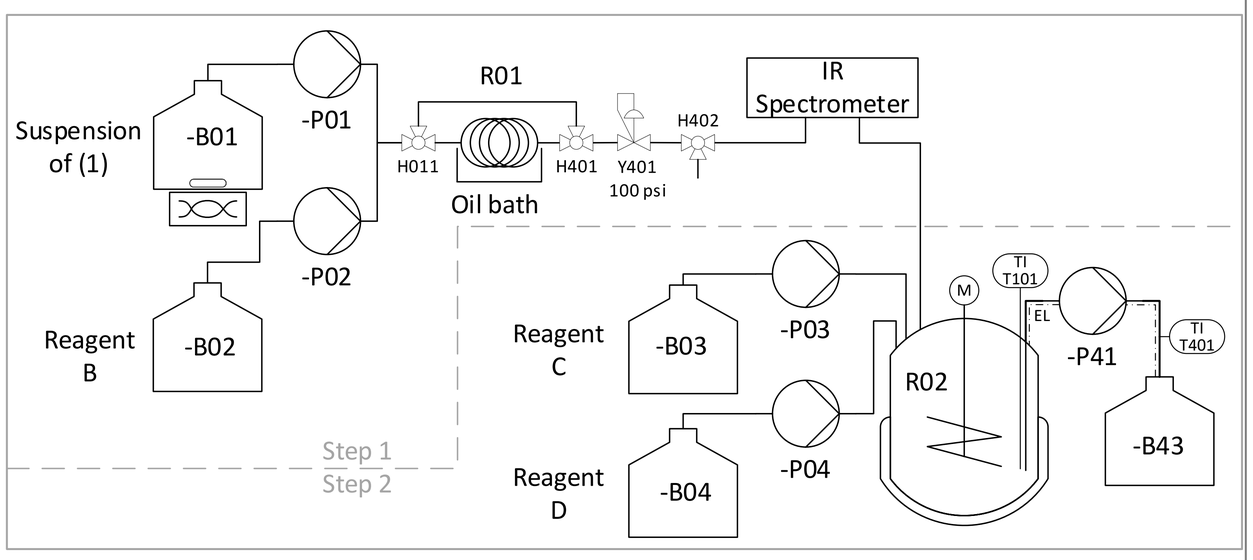

Figure 1 : Experimental set-up for the synthesis of (2) and CS-Amide in a PFR and CSTR reactor in series

	Batch mode	Continuous mode
Yield 1st step	81.8%	88.2%
Yield 2nd step	91.1%	89.1%
Global yield	74.5%	78.6%
Space Time Yield 1st step	3.3 g/l/min	25.2 g/l/min
Space Time Yield 2nd step	1.2 g/l/min	7.5 g/l/min

Table 1 : Comparison between batch and continuous mode for the synthesis of (2) and CS-Amide

CONCLUSION

With limited numbers of experiments, both steps have been optimized and their productivity improved compared to the batch mode.

This project can still evolve by testing other technologies for continuous synthesis. Furthermore, it will be possible to implement the purification and isolation of CS-Amide in continuous mode to transform the whole process into continuous mode.

In view of a scale-up of the process there are several points to consider such as the preparation and pumping of a homogeneous suspension (choice of the right agitator and pumps), the first reactor works under pressure (6.8 bars), the second stage is in a biphasic system (choice of the agitator to avoid decantation) and increase of the production scale by scaling-up or scaling-out.

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