

Endpoint Detection of a Hydrogenation Sampling Reactions at Elevated Pressure



Based on studies by **Sonja Kamptmann, Novartis**

Automated sampling of a hydrogenation reaction at 5 bar pressure improved product quality by enabling the study of the mechanism of formation of an undesired by-product.

Hydrogenation reactions require continued monitoring to eliminate over-hydrogenation that leads to a high level of undesired by-products and impurities. This hydrogenation reaction at Novartis required understanding of the mechanism of formation of a critical by-product. Studies included confirmation of which reaction step and parameters force its formation. The goal was to develop a process for the production of high quality product with less than 0.12 mass-% of the critical by-product.

Sampling hydrogenation reactions using traditional sampling techniques is a multi-step and time-consuming process, making it error-prone and difficult to perform reproducibly. Reactions typically run for several hours and manual sampling leads to missing data for the 8 to 16 hour period. Also, manual sampling processes interfere with reaction progression, thus affecting reaction kinetics. These challenges require many repeat experiments to gain the information necessary for good process decisions.

The automated sampling capabilities of EasySampler overcome these sampling difficulties. A sequence was programmed to sample this 2-step hydrogenation reaction every 10 minutes, for a period before and after the expected reaction end-point. All samples were then analyzed by HPLC.

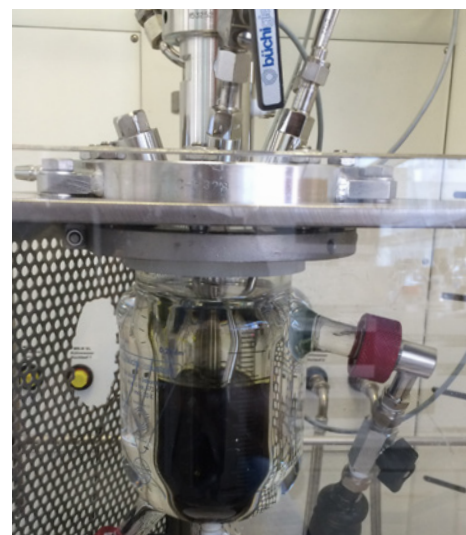


Figure 1. Hydrogenation reaction with EasySampler probe

Results

The reaction profile shown in Figure 2 indicates that formation of the critical desalkoxy-3 by-product (green) starts immediately after the starting material (blue) is depleted. The by-product increase at 10h19m confirms that the by-product formation is triggered by the reaction with hydrogen. To suppress the desalkoxy-3 formation the reactor was pressurized with nitrogen (grey line). Based on these results and further experiments using EasySampler's automated sampling capabilities (data not shown), Novartis was able to define a stop criterion for the reaction based on the hydrogen uptake of the reaction. This stop criterion is successfully used to end the hydrogenation at the right moment, where the reaction is completed, and only low-level acceptable amounts of by-product have been formed.

Conclusions

By introducing automated, unattended sampling, with EasySampler, Novartis was able to take representative samples of this hydrogenation reaction for the first time. The high quality samples generated quality data to provide accurate reaction information for improved reaction understanding to develop a process to maximize product yield and quality.

"EasySampler significantly facilitated sampling hydrogenation experiments and allowed monitoring over longer reaction times."

Sonja Kamptmann, Novartis

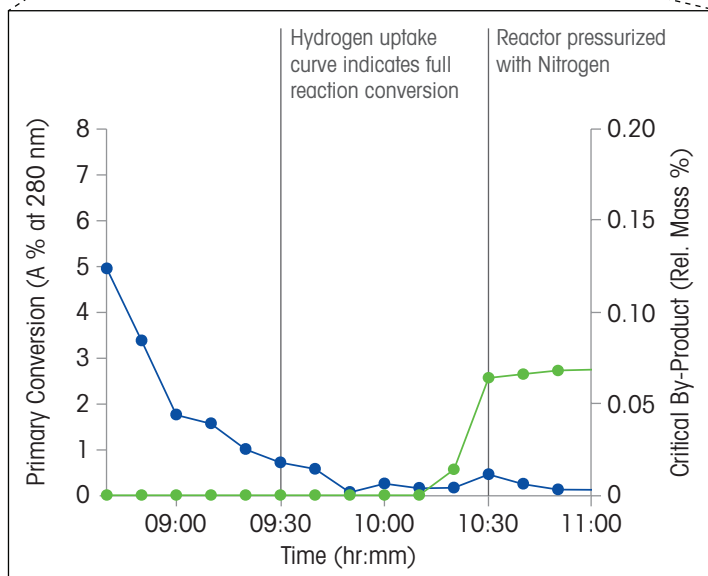
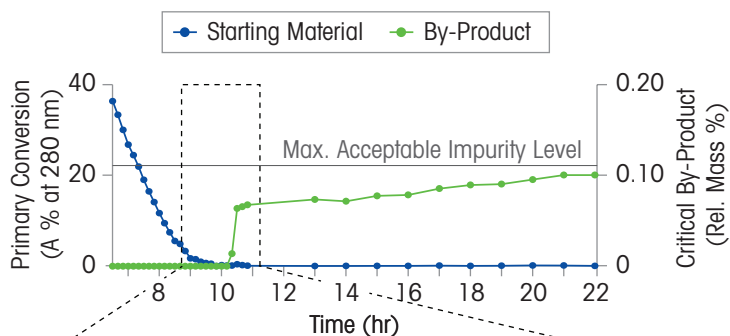


Figure 2. Reaction profile determined by HPLC analysis of samples acquired by EasySampler confirms that the onset of critical by-product (green) formation coincides with depletion of the starting material (blue).

EasySampler: Unattended, Representative Sampling



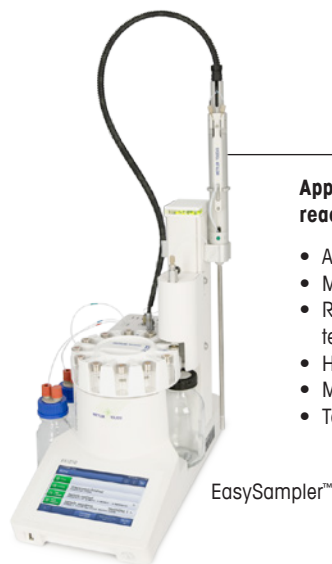
Difficult to Sample Reactions

Eliminate time-consuming and error-prone manual sampling methods.



Automated and Unattended

Continued unattended sampling operations to gain a complete data set for the duration of the reaction, without affecting reaction progression.



Application of EasySampler in other reactions that are difficult to sample:

- Air-sensitive reactions
- Moisture-sensitive reactions
- Reactions at sub-ambient temperature
- Heterogeneous reactions
- Multi-phase reactions
- Toxic reactions

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