Application Note

Impurity Profiling of an Ullman Reaction

Sampling Viscous Slurries

Based on studies by **Kristin Wiglesworth** and **David Place, Pfizer**

Reaction progress analysis of information-rich experiments enables better reaction understanding for good process decisions to maximize product yield and quality.

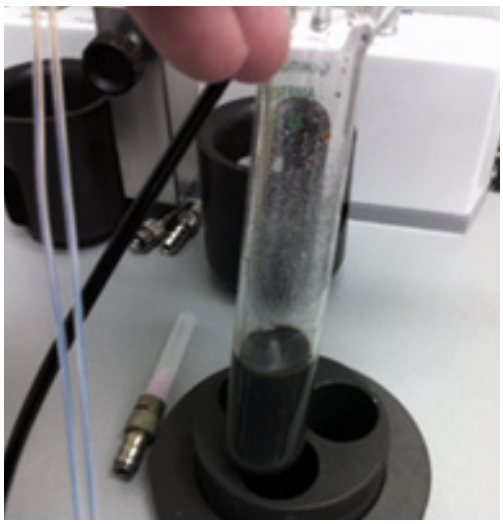
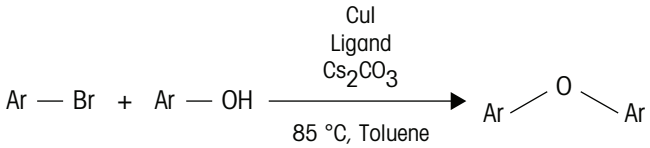


Figure 1. Dark Ullman reaction mixture in an EasyMax tube reactor

To test the sampling capabilities of EasySampler, scientists at Pfizer selected the Ullman Reaction since it is a reaction that is typically cumbersome to sample manually. It is a dark mixture with known insoluble reagents, making it difficult to see what was being sampled, as well as, easily clogging manual sampling tools. The reaction solution changes consistency over the course of the experiment, thickening as the cesium carbonate disperses, making it difficult to sample accurately and reproducibly. In addition, sampling is needed over a 30 hour period, so the unattended sampling capabilities of EasySampler were required.

EasySampler was inserted into a 10 mL glass tube reactor in an EasyMax synthesis workstation, and captured samples overnight at pre-programed time intervals. Scientists optimized the quench solvent to 1 v/v % water in DMSO to ensure complete dissolution of all reaction components, and to be ready for accurate offline analysis.



METTLER TOLEDO

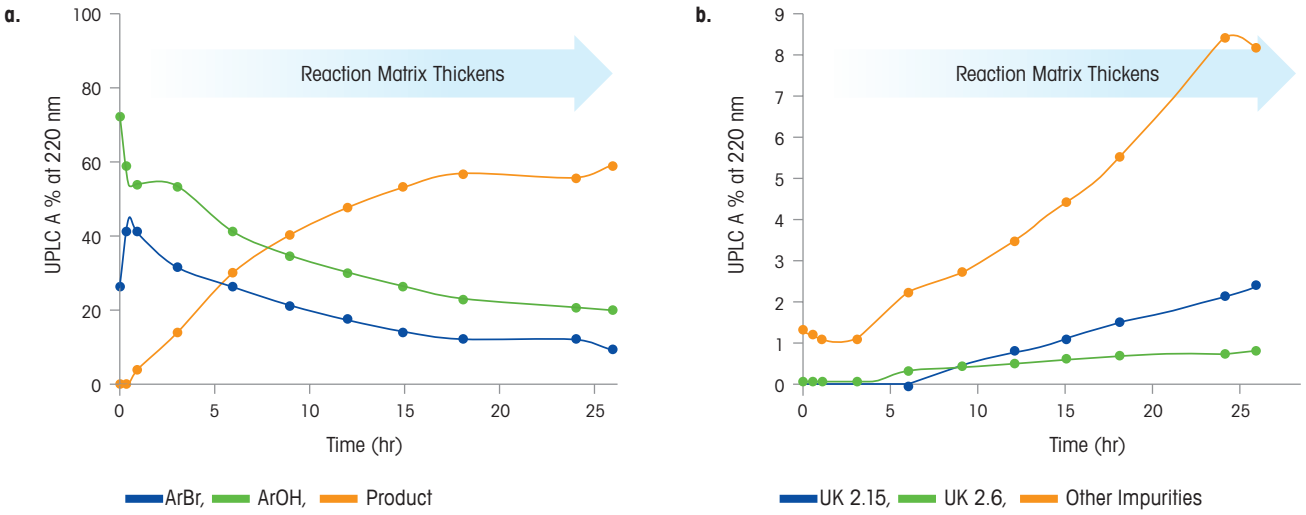


Figure 2. Progression of the Ullman reaction monitored by analysis of conversion (a) and impurity (b) profiles gained by UPLC analysis of representative samples acquired by EasySampler over 30 hours.

Results

EasySampler successfully sampled this thick, dark Ullman reaction, and provided representative reaction samples throughout the 30 hour experiment. The conversion data shows that product formation stalls after 18 hours (Figure 2a), indicating the reaction reached its end-point. However, the low-level impurity profile shows impurity formation continues after 18 hours, through the course of the 30 hour reaction (Figure 2b). This information enables a good decision regarding the optimal time to stop the reaction in order achieve a permitted impurity level in the final product, while maximizing yield.

Conclusions

Using EasySampler, accurate reaction kinetics information and impurity profiles can be collected from reactions that are typically cumbersome to sample, such as the highly viscous Ullman reaction. In addition, this study clearly shows that by using EasySampler, information rich experiments provide the means for monitoring reaction progress to effectively assign a reaction end-point to maximize product yield and quality.

EasySampler™

EasySampler: Unattended, Representative Sampling

Representative and Reproducible
Sample heterogeneous reactions with confidence – a sample, including solids, fills a sampling pocket of fixed volume to provide highly reproducible samples.

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:

- Moisture-sensitive reactions
- Reactions at elevated pressure
- Reactions at sub-ambient temperatures
- Heterogeneous reactions
- Multi-phase reactions
- Toxic reactions

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