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BEYOND PROCESS CHEMISTRY

Process Development Case Study
EXPERIMENTAL DESIGN
Optimisation of an Acid-mediated Rearrangement with DoE

INTRODUCTION
Significant development of a carbon skeleton rearrangement reaction was required as a critical step in the proposed manufacturing route for an active pharmaceutical ingredient (API). The initial procedure employed an acid as solvent (0.4 M) and an alcohol as nucleophile (18 eq.) with the substrate heated at 95 °C in a sealed tube. The work-up utilised a very dilute quench, multiple extractions, concentration to dryness and column chromatography for purification. This provided the product in 70% yield and purity of >99 area% by UPLC.

AIM
The goal of this study was to optimise the reaction conditions for suitability on multi-kilogram scale. Key was obtaining the product in high yield and purity, minimising formation of side-products, decreasing the temperature of the process to circumvent use of a sealed vessel and reducing the volume of the acid (solvent) to avoid the dilute work-up. A formal experimental design approach (DoE) was exploited to fully explore the reaction space and understand the impact and interdependency of the main parameters on the performance of the process.

PRE-DoE STUDIES
Preliminary studies on the rearrangement reaction revealed three key parameters that affected the outcome: **volume of acid**, **alcohol stoichiometry** and **temperature**. The resulting process used a 0.4 M concentration of acid with 9 eq. of alcohol at 65 °C in an open vessel. These conditions resulted in 93.4% of the requisite product, 4.3% Impurity 1 and 0.9% Impurity 2. This proved acceptable since both impurities could be purged by recrystallisation.
The work-up procedure was also improved by replacing the dilute extractions with an aqueous drown-out of **80 rel. vol. water**, followed by addition of 11 rel. vol. aqueous inorganic base solution. This also served to quench the acidic reaction mixture. The large volume of water was shown to be required to ensure smooth precipitation of the product during addition of the base. Lower volumes of water in the work-up led to poor physical form in the isolated product. Further development work was focused on **decreasing the volume of acid** required for the reaction, and therefore the volume of water required for a successful drown-out.

DoE INVESTIGATION
In the DoE study the key parameters (concentration in acid, alcohol stoichiometry and temperature) were each investigated at three levels. The settings were chosen based on the data obtained from the pre-DoE studies (**Table**).

Parameter	Low	Middle	High
Alcohol (eq.)	4.5	9.0	13.5
Concentration in acid (M)	0.4	0.6	0.8
Temperature (°C)	55	65	75

Table – Parameter settings for the DoE study

For these three variables, a standard design of 16 experiments plus three replicates to check reproducibility was carried out. Three responses at the end of the reaction (EOR) were captured: area% of desired product, area% Impurity 1 and area% Impurity 2, each as determined by UPLC-MS.

DoE RESULTS
The outcome of the DoE studies is presented in a series of plots, **Figures 1-4**. Each plot illustrates the correlation between the **level of the desired product** (%, in **red**) and the two key reaction parameters at the specified temperature. Also shown is the **level of Impurity 1** (%, in **green**) and the **level of Impurity 2** (%, in **blue**).

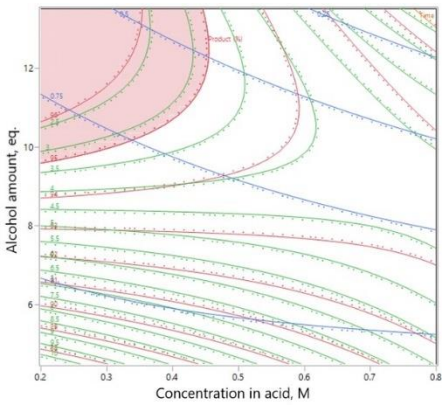

Figure 1: Correlation at 65 °C. Pink area >95% product.

At 65 °C, the quantity of the desired product increases with higher equivalents of the alcohol and lower concentration (larger volumes of the acid). The level of Impurity 1 also clearly decreases in the same direction (**Figure 1**). Impurity 2, however, decreases with higher concentrations and higher equivalents of the alcohol. >95% product formation (**Figure 1**, highlighted in pink) does not occur under the higher concentrations in the acid with best results not far from 0.4 M or less – conditions necessitating >100 rel. vol. in the subsequent work-up.
From the pre-DoE studies it was found that successful crystallisation could be obtained from reaction mixtures with >93% product (**Figure 2**, pink). This can be

achieved with increased concentration of acid, up to 0.8 M. The level of Impurity 1 is maintained at <4.5%, the level of Impurity 2 at <0.75% (both acceptable for the following crystallisation).

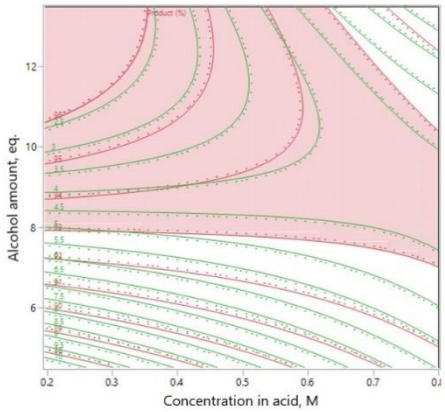

Figure 2: Correlation at 65 °C. Pink area >93% product.

Optimal alcohol stoichiometry for 93% product at 0.8 M concentration was 9 eq. The reaction space thus described for this doubly concentrated process is wide (and flat), which is indicative of a more robust process. Similar trends are observed at 75 °C, although the areas of >95% product and >93% product (**Figure 3**) are shifted towards the lower concentrations proportionately. This is not in the interest of reducing the volume of the acid for the reaction and water for the work-up, therefore increasing the temperature to 75 °C is not beneficial.
At 55 °C results were again similar to those at 65 °C. Although the >93% product area reaches 0.8 M concentration at 55 °C (**Figure 4**), >95% product is only achieved at less than 0.5 M concentration. This indicates that performing the process at 55 °C under higher concentrations will not provide any more of the desired product. Furthermore, reactions at 55 °C were also slower than at 65 °C and so there is no benefit in decreasing the temperature.

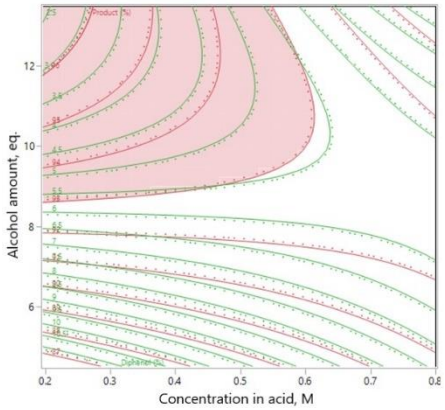

Figure 3: Correlation at 75 °C. Pink area >93% product.

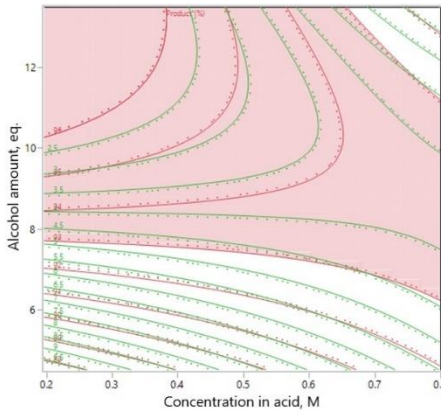

Figure 4: Correlation at 55 °C. Pink area >93% product.

CONCLUSIONS

The experimental design (DoE) studies described herein efficiently and effectively explored the reaction space described by three critical factors. A comprehensive understanding of the correlation between these three parameters was obtained. Accordingly, the process was optimised and its robustness established.
In summary, it is possible to double the concentration in acid up to 0.8 M without decreasing the beneficial conversion to product (>93% area by UPLC). Optimal conditions for this doubly concentrated process are thus: 0.8 M concentration in the acid at 65 °C with 9 eq. of alcohol. This furnishes 93.1% of the desired product, 4.7% of Impurity 1 and 0.3% of Impurity 2.
Furthermore, the work-up volumes were successfully reduced from 100 rel. vol. down to 45 rel. vol., of significant importance in the development of a scalable manufacturing process. Optimisation of the work-up regime was enabled in a concise manner by performing only 16 experiments wherein multiple parameters were varied simultaneously.