FROM BATCH TO FLOW: MODELLING-DRIVEN OPTIMIZATION OF VILSMEIER FORMYLATION

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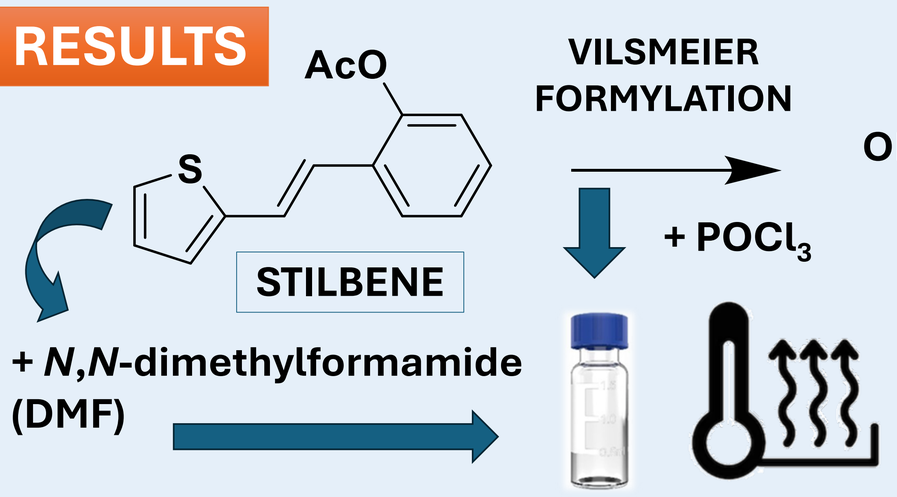
INTRODUCTION

In recent years, considerable attention has been directed toward developing compounds to treat neurological disorders such as Alzheimer's and Parkinson's disease, as well as to counteract organophosphate poisoning from pesticides and nerve agents [1]. Oximes are of particular interest for their ability to reactivate acetylcholinesterase and butyrylcholinesterase, enzymes inhibited in these conditions. Such oximes can be prepared from stilbenes *via* a two-step route starting with formylation, commonly achieved through the Vilsmeier reaction [2]. This highly exothermic process poses safety risks in batch mode, whereas continuous millireactor systems provide superior heat control and improved process safety [3].

EXPERIMENTS AND RESULTS

Initial Batch Experiments



Initial small-scale batch (vials, 2 mL volume) experiments were conducted to assess the effects of temperature, $POCl_3$ amount, and the concentration of the stilbene in the reaction. All three parameters were found to strongly influence reaction rate and product formation, with higher temperatures (>100 °C) also accelerating degradation.

Mathematical Modelling

A second-order kinetic model with Arrhenius temperature dependence was established based on concentration–time profiles from batch experiments at five temperatures (25-100 °C). The model was then expanded to include impurity formation, with additional high-temperature experiments (100-140 °C) enabling estimation of kinetic parameters for the degradation. The model was subsequently validated in independent experiments (figure on the right).

MicroMath Scientist software package

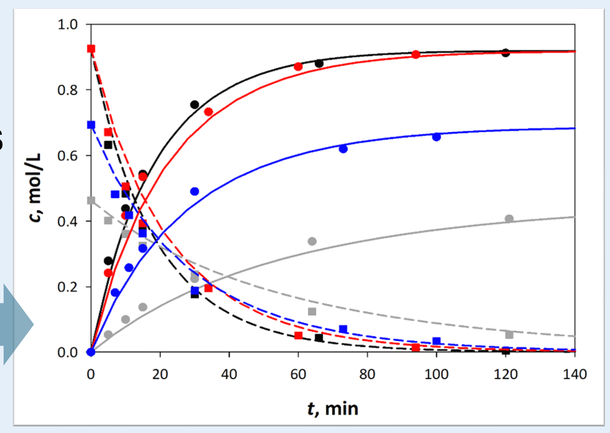
KINETIC PARAMETERS ESTIMATION

2nd order reaction rate:

$$v = k \cdot c_{\mathrm{R}} \cdot c_{\mathrm{POCl_3}}$$

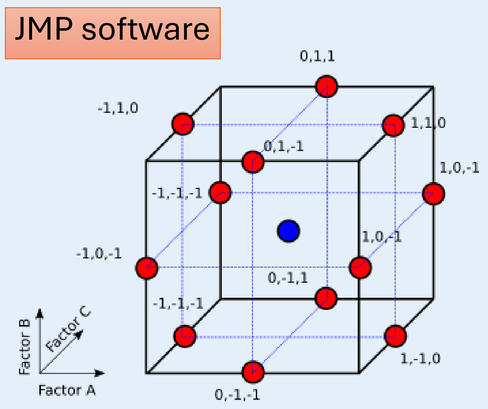
Arrhenius equation:

$$k = A \cdot e^{-\frac{E_a}{R \cdot T}}$$



Process Optimization

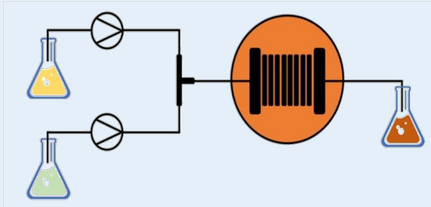
JMP software



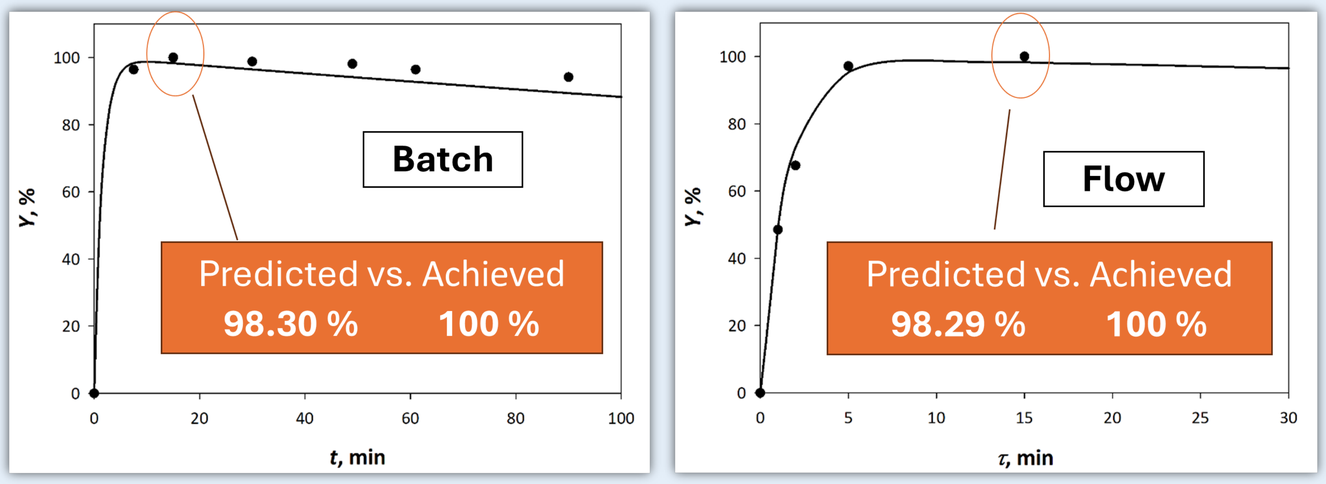
Model-based optimization was performed using a Box–Behnken design to evaluate the effects of temperature, $POCl_3$ equivalents, and the concentration of stilbene on the 15-min yield. Statistical analysis of the simulation data identified significant linear, quadratic, and interaction terms, confirming that the RSM model accurately reflects the behavior of the mechanistic model ($R^2 = 0.94$). Solving the fitted polynomial provided optimal batch conditions for maximizing the yield.

OPTIMAL BATCH CONDITIONS:
✓temperature: 96 °C
✓$POCl_3$ quantity: 6.5 mol eq
✓stilbene concentration: 0.85 mol/L

Flow Experiments



A validation experiment under the predicted optimal batch conditions showed excellent agreement with the simulated profiles, after which the mathematical model was modified for application in a millireactor to simulate yields at different residence times. The adapted model was then validated across multiple residence times in a millireactor with a 1 mm tube diameter.



2.8 mg/min **PRODUCTIVITY** **4.6 mg/min** ✓

Conclusion

In this study, the Vilsmeier formylation of a stilbene compound was investigated and optimized using a mathematical modelling approach to facilitate transfer to a continuous-flow reactor. The model was developed based on batch experiments and successfully validated in both a batch reactor and a continuous millireactor. Under optimized conditions, the process exhibited significant improvements in efficiency, while the continuous-flow process enhanced safety compared to batch operation due to improved thermal control.

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References

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