Abstract

The doctoral dissertation presents the development of an autonomous, self-optimizing microflow system, experimentally validated on the Claisen–Schmidt condensation between 2-methoxybenzaldehyde and acetone. The aim was to establish a faster, more efficient, and more sustainable approach for optimizing complex, multistep reactions sensitive to process conditions. Due to the limitations of classical methods (one-factor-at-a-time, DoE), we designed an integrated system combining flow chemistry, process analytical technologies (PAT), and artificial intelligence. The system is based on a microflow reactor with a FlowPlate reaction module, two PAT techniques (inline FTIR and online UPLC), and the multi-objective optimization algorithm TSEMO. Python-based software, using DLL and OPC UA protocols, implements a master/slave architecture for connecting and controlling components, enabling precise automated regulation of reaction conditions, steady-state detection, and triggering of UPLC analyses.

The model reaction proceeds in two steps, with the second being kinetically limiting. A two-step kinetic model was developed, allowing reliable prediction of reaction conditions while accounting for the temperature and concentration dependence of both the intermediate (enone) and the final product (dienone). Despite its lower activation energy, the second step proved rate-limiting due to a lower pre-exponential factor, requiring precise control of the intermediate balance. The system rapidly converged to optimal conditions; the highest dienone content achieved was 69.1% (UPLC area %), with an average deviation of 7.5%. Experimental results were validated against model predictions, showing agreement within ±10.

The results demonstrate that complex chemical reactions can be conducted and optimized without manual intervention. The system is modular and scalable, enabling straightforward integration of new devices and methods, while reducing development time and reagent consumption. Its autonomy ensures faster identification of optimal conditions, improved safety, and reproducibility, contributing to the digitalization of future laboratories.

The innovation was awarded the gold prize by the Chamber of Commerce of Dolenjska and Bela krajina.

Key words: Flow chemistry, Self-optimization, Machine learning, Bayesian optimization, Claisen-Schmidt condensation, Self-optimization validation, Chemical kinetics, Mathematical modeling, Mathematical programming, Process design, Process control, Process monitoring