Microwave flow chemistry : Single-mode system for kg-scale organic synthesis

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Single-mode system for kg-scale organic synthesis

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Abstract — **The optimization of single-mode microwave-assisted flow reaction conditions was investigated by improving sampling efficiency through microwave power gradients and in-line analysis, and advanced prediction through response surfaces. Application to kg-scale organic transformations highlights the utility of this protocol.**

Index Terms — **microwave heating, optimization, flow reaction, in-line analysis, response surfaces**

I. INTRODUCTION

Microwave-assisted organic chemistry has allowed the academic revival of many synthetic transformations previously considered synthetically useless under extreme conditions [1]. However, efficient microwave heating is significantly limited by the penetration depth of the microwaves, thus facilitating industrial scale-up. A reasonable solution to this issue is the employment of the flow method, in which the reaction is carried out continuously using a pump and tubes. The reactor for the flow method is not a flask but a tube to meet the microwave penetration depth requirements (Fig. 1a). Microwave flow reactions have been well demonstrated to have many advantages in reaction rates, yields, and scale-up [2]. In particular, the recent development and commercialization of resonator-type single-mode microwave reactors equipped with solid-state microwave power supplies have enabled synthetic chemists to use this technology as a familiar tool (Fig. 1b, left). Furthermore, microwave flow chemistry is developing rapidly due to an auto-tuning function to automatically maintain the optimum resonance frequency (Fig. 1b, right).

Optimizing reaction conditions is one of the most critical issues in maximizing resource efficiency and productivity and minimizing waste, cost, and environmental impact. Many organic chemists often use the OVAT (one variable at a time) method, in which one particular variable is varied while the other variable is fixed [3]. The disadvantage of this method is the inability to thoroughly examine all correlations among variables, resulting in deceptive optimal values. The response surface method (RSM) is an alternative to compensate for this issue by providing an optimal solution on a response surface that approximates the objective function (yield, productivity, selectivity, etc.) with a few data points [4].
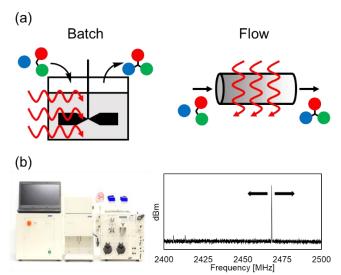

Fig. 1. (a) Microwave batch and flow reactions, (b) Microwave-assisted flow reactor system and its frequency characteristics
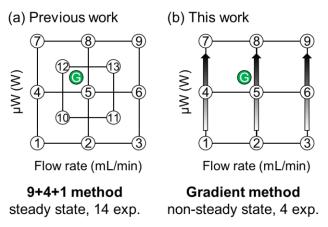

Fig. 2. Microwave-assisted flow condition optimization methods

Recently, we developed an RSM-based optimization of microwave flow conditions, termed the "9+4+1 method" [5]. In this protocol, the first nine reactions (Fig. 2a, 1-9) covering the feasible region within the instrument limitations were performed at steady-state conditions, and each yield was determined by GC analysis. Then, four reactions (Fig. 2a, 10-

13) were sequentially run, focusing on the conditions with the highest yields to improve the accuracy of the optimal conditions. From the 13 data obtained, a quadratic polynomial model was utilized to create a response surface to predict the optimum conditions. The predicted optimum conditions were studied, and optimization was achieved for two factors (flow rate and microwave power). Since microwave absorption efficiency varies depending on the substance, temperature, and equipment, the conventional method had difficulty optimizing conditions; however, this protocol enables optimization of microwave output and has achieved yields of up to 99% in a single flow line. While this methodology is undoubtedly appropriate, the experiments are conducted under steady-state conditions, which take time to stabilize and wastes reagents. This study applied microwave output gradient variation and in-line analysis to realize efficient data sampling and improve the rapidity and accuracy of optimization of the flow reaction conditions (Fig. 2b). In addition, multiple machine learning models were used to prepare response surfaces to improve prediction accuracy with a minimum of experimental operations.
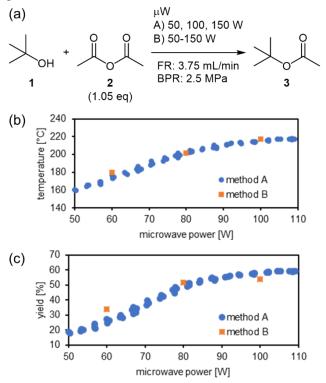

Fig. 3. Comparison of steady-state (method A) and gradient condition (method B) using acetylation of *tert*-butyl alcohol (a). A plot of microwave power to temperature (b) or yield (c).
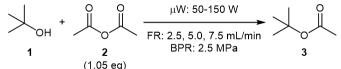
II. RESULTS AND DISCUSSION

We started to assemble a system to continuously acquire data under gradient conditions. Since our laboratory focuses on developing synthetic methods for process chemistry, a high concentration of reaction mixture is desirable to maximize productivity. A flow-type near-infrared (NIR) system limited to

the third harmonic region was selected for in-line analysis because of its high transmission ability, which hardly saturates the spectrum even under neat conditions. The acetylation of *tert*-butyl alcohol (**1**) with acetic anhydride (**2**) was performed in a microwave flow reactor equipped with a flow NIR detector to demonstrate the feasibility of the gradient method. Microwave power was varied by gradient method (50–110 W for 10 min (method B)), and outlet temperature and yield were compared with steady-state conditions of 60, 80, and 100 W (method A), showing good agreement (Fig. 3). We thus considered the gradient conditions under microwave heating to be quasi-steady. The advantage of rapid microwave heating should help in rapid optimization, as the temperature follows the rapid change in microwave power even in a short time (10 minutes).

With a method for continuous data acquisition under gradient conditions, the optimization of two variables and three levels of gradient flow reaction conditions for the acetylation reaction of *tert*-butyl alcohol (**1**) was investigated (Table 1). Two variables, microwave power and flow rate, were optimized with 1.05 equivalents of acetic anhydride (**2**) and 2.5 MPa back pressure as constant values. First, reaction conditions were optimized using the steady-state 9+4+1 method (Fig. 2a) for comparison. Each acquisition time was set to 10 minutes, including the time to reach a steady state and collect NIR-yield data. A total of 13 experiments were conducted with microwave power ranging from 50-150 W and flow rates from 2.0-8.0 mL/min due to the specifications of the microwave flow system (Table 1, entries 1-4). From the results of 13 steady-state reaction studies, data (acquisition time: 13 × 10 min) predictive models were obtained using multiple linear regression (MLR), partial least squares regression (PLS), support vector regression (SVR), and random forest regression (RFR), and RSM predicted optimal values for the two variables (Fig. 4a). Reaction yields were converted to logit functions to predict 0-100% yields. Productivity was calculated from the yields and corresponding flow rates. The regression models were evaluated by the relative error (RE) between the predicted and experimental productivity after the actual flow reaction was performed under the predicted conditions. The RE values of the models using SVR were the lowest (Table 1, entries 1-4) and in good agreement with the overall test data (Fig. 4). However, the 9+4+1 method could not predict productivity beyond the input data, the prediction resulted in low accuracy due to the small number of data points.

Next, the gradient range was set to 50-150 W and the rising rate to 10 W/min, and a total of 242 data sets were acquired using the gradient method. All of the prediction models had high coefficients of determination for the training data. In particular, PLS and SVR showed higher productivity under the prediction conditions than the maximum of the training data (Table 1, entries 5-8). The RE was found to be lower for SVR. Under optimal reaction conditions predicted from data obtained in only three experiments, maximum productivity of 1.89 kg/d was achieved with a single flow line.

TABLE I. TWO-VARIABLE, THREE-LEVEL OPTIMIZATION FOR SYNTHESIS OF *TERT*-BUTYL ACETATE

Entry	No. of exp.	Model	Predicted				Observed	RE (%)[b]	Ratio[c]
			R[2] [a]	μW (W)	Flow rate (mL/min)	Productivity (g/min)	Productivity (g/min, kg/d)		
1	13	MLR	0.92	150	8.0	1.31	0.80, 1.15	39	0.63
2	13	PLS	0.44	150	4.0	1.43	1.12, 1.61	22	0.89
3	13	SVR	0.90	139	4.8	1.21	1.15, 1.66	5	0.91
4	13	RFR	0.92	126	6.2	1.40	1.03, 1.48	26	0.82
5	3	MLR	0.96	150	3.7	1.51	1.04, 1.50	31	0.89
6	3	PLS	0.91	150	5.3	2.46	1.30, 1.87	47	1.11
7	3	SVR	>0.99	134	5.5	1.17	1.31, 1.89	12	1.12
8	3	RFR	>0.99	128	6.2	1.45	0.93, 1.34	36	0.79

[a] Coefficient of determination, [b] Relative error, [c] Ratio of increase from maximum input data
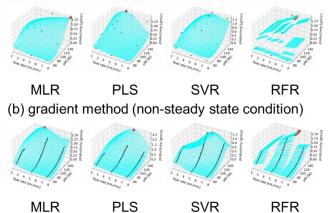

Fig. 4.   Response surfaces using input data of (a) steady-state conditions (corresponds to table 1, entries 1-4) and (b) gradient conditions (corresponds to table 1, entries 5-8). Black points represent experimental input data. Red points represent the predicted optimal conditions. Cyan points represent the response surface.

III. CONCLUSION

The optimization of single-mode microwave-assisted flow reaction conditions was investigated by microwave power gradient, in-line analysis, and SVR-response surface prediction to achieve kg-scale organic synthesis.

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