

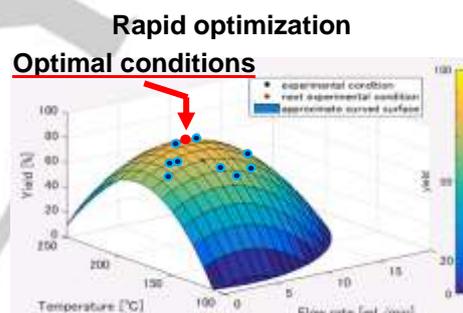
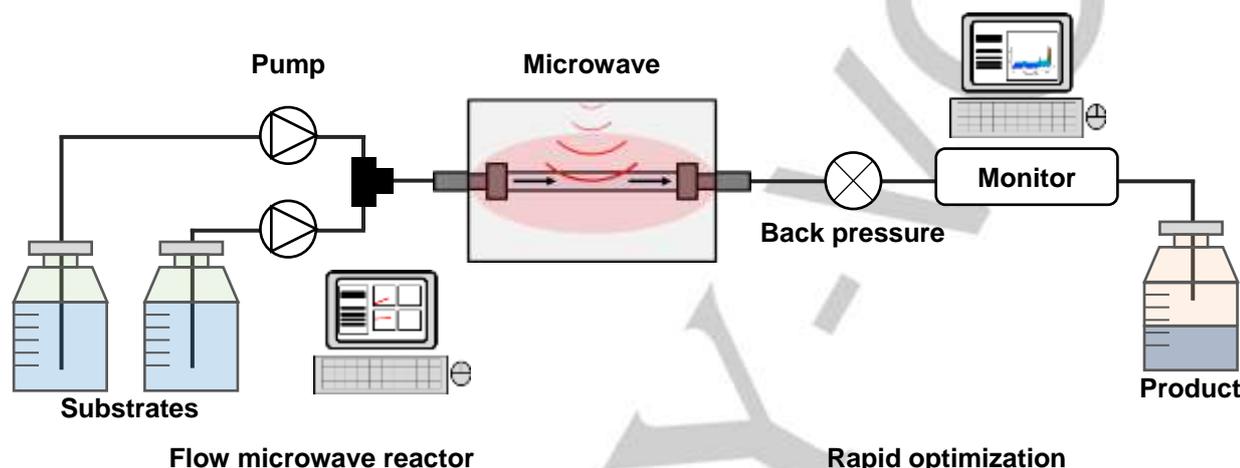
Rapid Optimization of Reaction Conditions Based on Comprehensive Reaction Analysis Using a Continuous Flow Microwave Reactor

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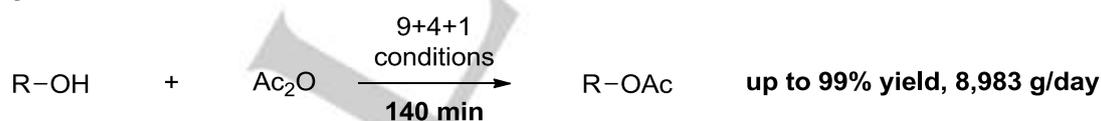
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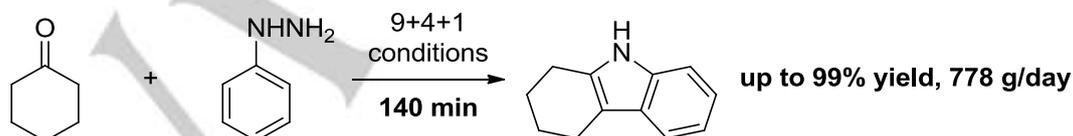
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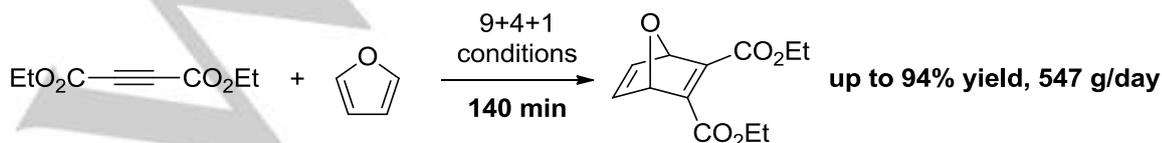
1. Acetylation



2. Fischer indol synthesis



3. Diels-Alder reaction



Abstract: Generally, the flow method has the advantage of a precise control over the reaction parameters and a facile modification of the reaction conditions, while a continuous flow microwave reactor allows for the quick optimization of reaction conditions owing to the rapid uniform heating. In this study, we developed a “9+4+1 method” to optimize reaction conditions based on comprehensive reaction analysis using a flow microwave reactor. The proposed method is expected to contribute to the synthesis of various fine and bulk chemicals by reducing cost and wastage, and by conserving time.

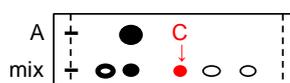
1. Introduction

Optimization has been one of the paramount issues throughout human history.^[1] With technological advancement, there has been an increasing demand for optimization methods that would lead to waste and cost reductions, as well as time conservation. Currently, optimization is necessary in all aspects of modern technology, from research and development to full-scale industrial manufacturing. In particular, in the pharmaceutical industry, optimization of conditions to reduce by-products and co-products is essential. For example, if stoichiometric substrates react to provide the desired product quantitatively, no purification process will be required. Furthermore, it is necessary that the process of optimization is as fast as possible.^[2,3]

In the conventional batch method, reagent preparation, reaction, purification, and analysis need to be performed during every optimization process (Figure 1). In contrast, in the flow method, immediate feedback by quick or real-time analysis may allow the rapid optimization of reaction conditions. In recent years, the applicability of continuous methods such as flow and stop flow methods to pharmaceutical manufacturing has been extensively studied.^[4] In addition, with the steady progress in modularization of equipment, many dangerous and complicated reactions are possibly carried out by the flow method.^[5] Therefore, the optimization of flow-based reaction conditions is imperative.

In 2002, it was noted that the design of experiments (DoE) should receive more attention from academia and industry.^[2,6] The number of publications that applied the DoE to various research and development in pharmaceuticals, materials, foods,

How to optimize the reaction?



Batch method

1 → 2 → 3 → 4 → 5 → 1 ...

Flow method

1 → 2 → (3) → 4 → 5 → 2 ...

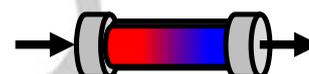
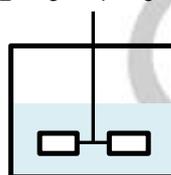
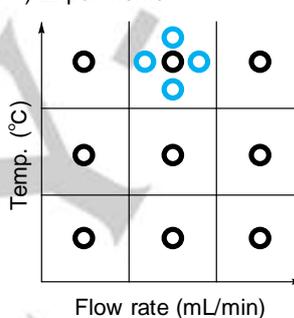


Figure 1. Optimization of reaction conditions.

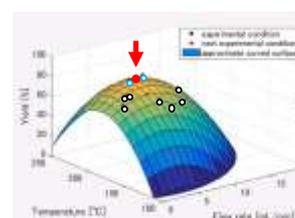
1) Experiments



● : 1st conditions (9)

● : 2nd conditions (4)

2) Surface approximation



● : Calculated (1)

Total 9+4+1 =
14 experiments

Figure 2. Our approach: “9+4+1 method” for rapid optimization.

and energy has dramatically increased.^[7–12] In this study, we developed a method, which combines experimental design and three-dimensional surface approximation, for the simple and rapid optimization of reaction conditions (Figure 2).

We believe that combining microwave heating with the flow method may lead to a more effective optimization of reaction conditions. Since its introduction to organic synthetic chemistry in 1986,^[13, 14] many advantages of the microwave method have been reported.^[15–17] It represents a direct heating method that enables uniform heating and higher temperature control, eliminates heat transfer time, and reduces reaction time.^[18] According to the Arrhenius equation, raising the reaction temperature is the simplest way to achieve a difficult transformation with a large activation energy. Although the penetration depth of the microwave is a drawback,^[19] the problem can be solved by combining it with the flow method.^[20] We utilized a microwave flow system (see frontispiece) that can monitor and control the reaction conditions and verify the optimization of basic and practical organic reactions.

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2. Results and discussion

The optimization technique developed in this work is called the “9+4+1 method”. It is an approach, in which the irradiation power and flow rate can be changed (Figure 2). Although this is a one-factor-at-a-time (OFAT) method, these two changeable factors provide valuable data because (1) they can be controlled easily and precisely, and (2) the irradiation power and flow rate greatly affect the reactivity and productivity. The herein developed method included the following procedure. The upper and lower limits of irradiation power and flow rate of the microwave flow system were equally divided into three, and overall nine points were optimized in order to eliminate the possibility of optimizing intentionally within a specific range (Figure 2, left). After analyzing the nine samples, the point affording the best yield was divided into four and four more experiments were carried out. A three-dimensional approximate surface was created from the 13 points of experimental data and a 14th experiment was performed according to the expected optimal condition (Figure 2, right).

When optimizing reaction conditions, the reaction temperature is generally used as an optimization factor. However, in this study, the microwave output was selected as the optimization factor, as it is difficult to measure and set an accurate internal temperature in a microwave reaction. The reaction temperature depends on the heat transfer occurring in the reactor and on the microwave absorption capacities of the substrate and solvent. Two three-dimensional surface approximations of the same acetylation reaction data are shown in Figure 3-a and b. As can be seen, neither of the surfaces is dome-shaped, which is necessary for optimization. Since the temperature increase by microwave heating depends on the reactants and solvents, surface approximation by temperature-flow rate-yield is not suitable (Figure 3-a). However, by choosing the appropriate threshold, an approximation by microwave power-flow rate-yield (Figure 3-b) can provide the desired surface (Figure 3-c). Based on these arguments, we chose irradiation power and flow rate as our optimization factors.

To prove the usefulness of the “9+4+1 method,” acetylation reaction, Fischer indole synthesis, and Diels-Alder reaction were optimized in the absence of a catalyst. All reactions were carried out at a backpressure of 2.5 MPa using a 200-W flow microwave reactor developed by SAIDA FDS Inc.^[21]

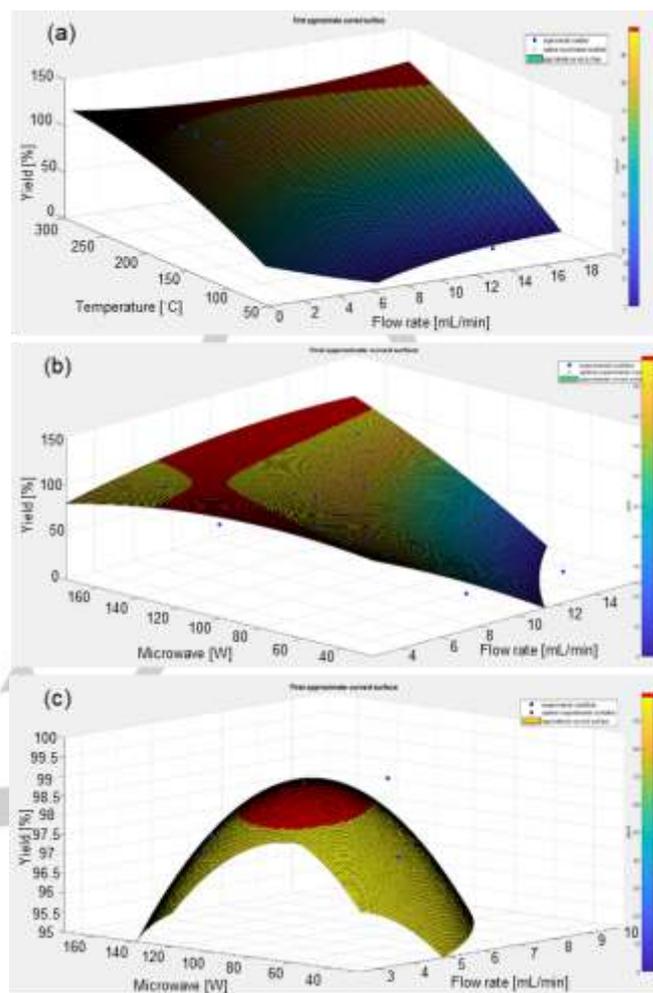


Figure 3. Three-dimensional surface approximation in acetylation of benzyl alcohol: (a) Temperature-Flow rate-Yield; (b) Microwave Power-Flow rate-Yield; (c) Optimized Microwave Power-Flow rate-Yield.

2.1. Acetylation reactions

Rapid optimization of acetylation reactions with various alcohols and 1.05 molar equivalents of acetic anhydride (**2**) was conducted in neat conditions. The results of acetylation of benzyl alcohol (**1a**) are summarized in Table 1. Since the 200-W flow microwave reactor operates in the range of 10 to 200 W at 0 to 20 mL/min, three points for each parameter, 50, 100, and 150 W, and 5, 10, and 15 mL/min for the irradiation power and flow rate, respectively, were set for the initial 9-point optimization. It took 10 min to investigate one reaction condition. The yield of acetylated product **3a** was quantified by GC. With the increasing flow rate to 15 mL/min, the reaction temperature and yield remarkably decreased (entries 1 ~ 3). Finally, acetylated product **3a** was obtained at 100 W and 5 mL/min with a maximum yield of 99% (entries 4 ~ 6). With the increase in irradiation power to 150 W, the acetylation reaction proceeded successfully, giving more than 96% yield at all the flow rates (entries 7 ~ 9). The region with the best yield (entry 4) was divided into four, and four more experiments were carried out (entries 10 ~ 13). A three-dimensional approximate surface was created from the 13 points of experimental data (Figure 3-b). However, the initial surface was inaccurate due to the large yield difference under each condition. By setting threshold values that exclude the low yield conditions, we attempted to optimize the high yield conditions. To create an approximate surface, we set the minimum number of data points to more than six. Eight of the 13 data points were used to create a domed surface. The 14th experiment was conducted according to the predicted optimum conditions (98 W, 5.1 mL/min), and **3a** was obtained with 99% yield (entry 14). The productivity under these conditions was 5,328 g/day. The volume of the reaction vessel is only 6.05 mL, and productivity of 5,328 g/day (1.9 ton/year) could be achieved with a single flow line. We demonstrated that the designed reaction could be optimized with only 14 experiments in 140 min.

Table 1. Results from the benzyl alcohol acetylation reactions.

$\text{BnOH } \mathbf{1a} + \text{Ac}_2\text{O } \mathbf{2} \xrightarrow{\mu\text{W-Flow}} \text{BnOAc } \mathbf{3a} + \text{AcOH } \mathbf{4}$ (1.05 eq)				
Entry	Microwave power [W]	Flow rate [mL/min] ^[a]	Temperature [°C] ^[b]	Yield [%] ^[c]
1	50	5 (73 s)	216	97
2	50	10 (36 s)	122	10
3	50	15 (24 s)	92	4
4 ^[d]	100	5 (73 s)	262	99
5	100	10 (36 s)	262	94
6	100	15 (24 s)	162	26
7	150	5 (73 s)	285	97
8	150	10 (36 s)	280	96
9	150	15 (24 s)	273	96
10	75	5 (73 s)	243	98
11	100	2.5 (145 s)	262	98
12	100	7.5 (48 s)	264	99
13	125	5 (73 s)	285	96
14	98	5.1 (71 s)	257	99

[a] Residence time in parentheses. [b] Outlet temperature. [c] Determined by GC. [d] Best yield conditions.

Table 2. Substrate scope in acetylation reactions.
$$\text{ROH} \quad + \quad \text{Ac}_2\text{O} \xrightarrow{\mu\text{W-Flow}} \text{ROAc} \quad + \quad \text{AcOH}$$

1
2
3
4

(1.05 eq)

Entry	R	Product	Microwave power [W]	Flow rate [mL/min] ^[a]	Temperature [°C] ^[b]	Yield [%] ^[c]	Productivity [g/day]
1	Bn	3a	98	5.1 (71 s)	257	99	5,328
2	Et	3b	134	6.5 (56 s)	248	99	5,112
3	Bu	3c	109	4.9 (74 s)	266	99	4,189
4	<i>i</i> -Pr	3d	87	4.5 (81 s)	250	99	3,564
5	<i>c</i> -Hex	3e	200	9 (40 s)	299	99	8,983
6	Geranyl	3f	50	2.5 (145 s)	170	99	2,532
7	<i>t</i> -Bu	3g	120	5.0 (73 s)	244	66	2,800
8	Ph	3h	125	5.0 (73 s)	270	99	5,129

[a] Residence time in parentheses. [b] Outlet temperature. [c] Determined by GC.

Our optimization method was applied to acetylation of other substrates as well (Table 2). Acetylation of primary (benzyl, ethyl, and butyl) and secondary (isopropyl and cyclohexyl) alcohols showed similar behaviors (entries 1 ~ 5). By using data exceeding the threshold, we could create an appropriate dome-shaped surface (Figure 3-c and Figure 4a-d). Acetylated products **3a–3e** were obtained in 97 to 99% yield according to the estimated optimization conditions. The productivity of cyclohexyl acetate **3e** exceeded 8,983 g/day (3.3 ton/year) despite the desktop-size reaction system, thus exhibiting excellent productivity (entry 5). Furthermore, interesting phenomena were observed in the case of geraniol and *tert*-butyl alcohol (entries 6 and 7). At high flow rates and low microwave power, the conversion and yield were low. In contrast, at low flow rates and high microwave power, the conversion rate was high. However, the yield decreased as the alcohol and acetate decomposed due to the prolonged

retention at high temperatures.^[22] For reaction optimization accompanied with the decomposition of substrates or products, a semi-tubular surface having a ridge from low to high flow rate and microwave power was formed, and a dome shape could not be constructed (Figure 4e-f). However, the range of conditions affording high yields could be identified. In the case of phenol, it was impossible to create a surface, as two conditions resulted in 99% yield in the investigation of the first nine conditions (Figure 4g). Nevertheless, the reaction proceeded quantitatively under a low flow rate and high power conditions (entry 8). In the conventional method, although it was common to set optimum conditions for each reaction, optimizing each substrate was a troublesome task. However, our “9+4+1 method” could easily set optimum conditions for each substrate.

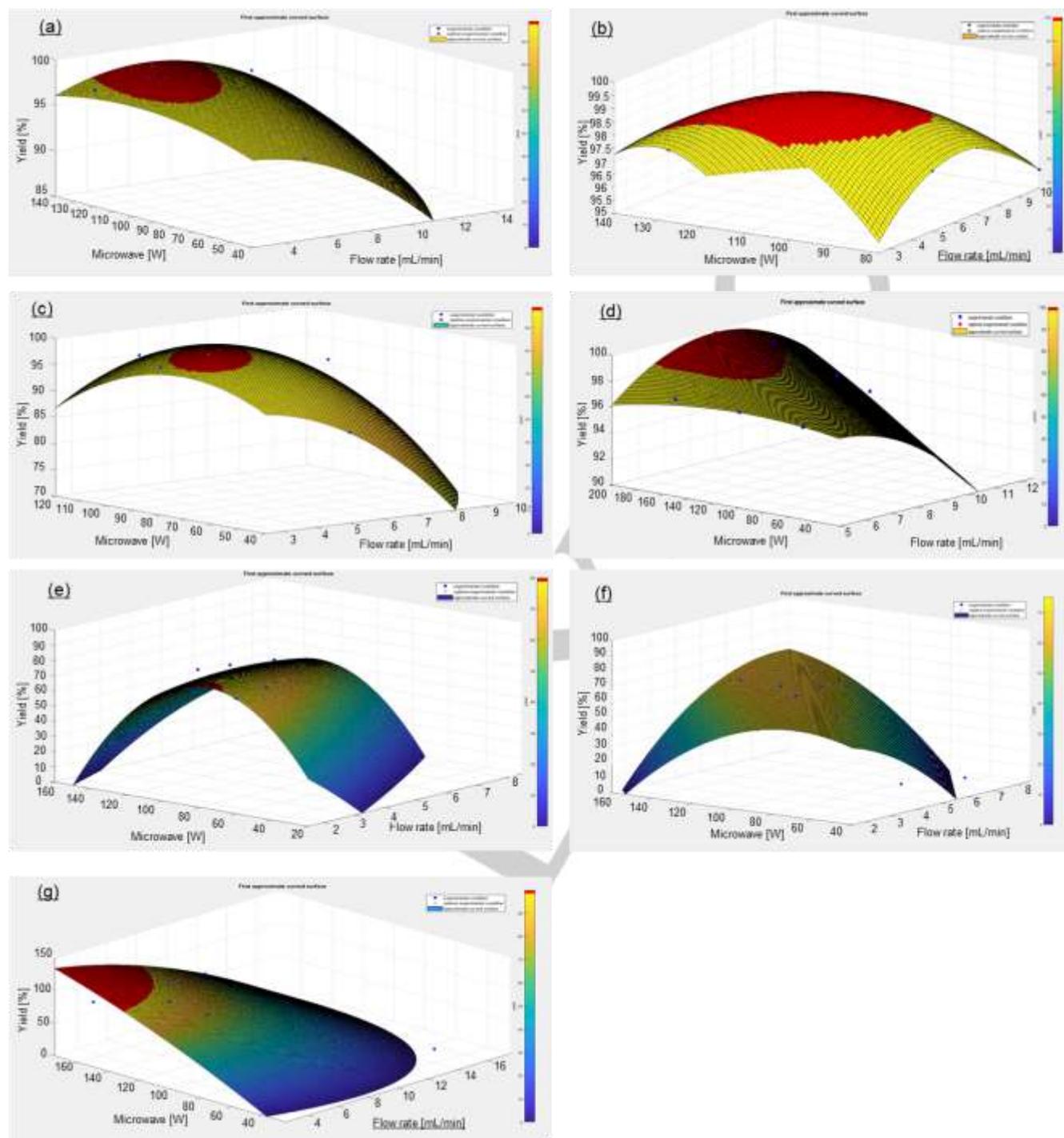
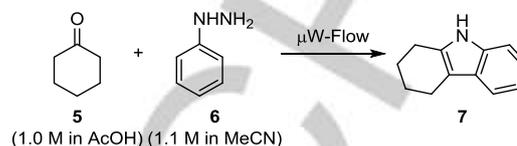


Figure 4. Three-dimensional surface approximation in acetylations: (a) ethyl acetate, (b) butyl acetate, (c) isopropyl acetate, (d) cyclohexyl acetate, (e) geranyl acetate, (f) *tert*-butyl acetate, and (g) phenyl acetate.

2.2. Fischer indol reactions

Recently, Akai *et al.* investigated 24 conditions using a microwave flow reactor and reported that indole (**7**) can be synthesized at a maximum yield of 83% (150 W, 232 °C, 13 mL/min).^[21] Interested in optimizing this reaction even further, we applied the “9+4+1 method” to this Fischer indole synthesis^[23] (Table 3). A 1.0 M solution of cyclohexanone (**5**) in acetic acid and a 1.1 M solution of phenylhydrazine (**6**) in acetonitrile were separately pumped at the same flow rate and mixed in a mixer located upstream of the reaction tube. All conversions based on the consumption of ketone **6** were 99%; however, at low temperatures, the yield of indole **7** was low. Generally, indole synthesis involves a stepwise reaction, and the cyclization reaction proceeds after hydrazone formation. At a low temperature, the reaction stopped in the first hydrazone formation step. As the temperature inside the reaction tube increased, the reaction solution started to boil, and the yield decreased due to the unstable microwave irradiation. Nine of the 13 data points were used to create a domed surface (Figure 5). The 14th experiment was conducted according to the predicted optimum conditions (134 W, 6.4 mL/min), and **7** was obtained with 99% yield (entry 14). The productivity under this condition was 778 g/day (284 kg/year), which can be achieved with a single flow line. Indole **7** was obtained in a quantitative yield exceeding the reported value (83%) by condition optimization of 14 experiments over 140 min, which indicates the usefulness of the present method.

Table 3. Results from the Fischer indol synthesis.



Entry	Microwave power [W]	Flow rate [mL/min] ^[a]	Temperature [°C] ^[b]	Yield [%] ^[c]
1	50	5 (73 s)	139	64
2	50	10 (36 s)	88	17
3	50	15 (24 s)	70	16
4 ^[d]	100	5 (73 s)	237	97
5	100	10 (36 s)	163	53
6	100	15 (24 s)	119	30
7	150	5 (73 s)	259	93
8	150	10 (36 s)	227	88
9	150	15 (24 s)	167	35
10	75	5 (73 s)	207	88
11	100	2.5 (145 s)	258	91
12	100	7.5 (48 s)	214	82
13	125	5 (73 s)	251	93
14	134	6.4 (57 s)	247	99

[a] Residence time in parentheses. [b] Outlet temperature. [c] Determined by GC. [d] Best yield conditions.

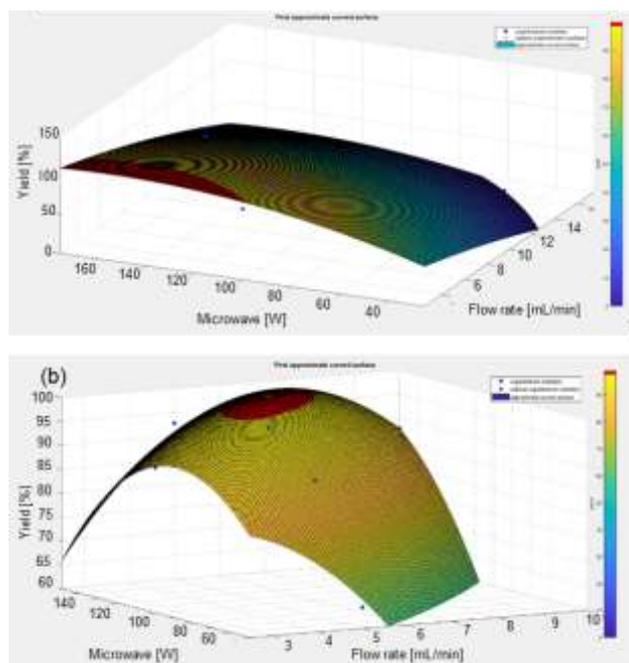


Figure 5. Three-dimensional surface approximation in Fischer indol synthesis: (a) Microwave Power-Flow rate-Yield; (b) Optimized Microwave Power-Flow rate-Yield.

2.3. Diels-Alder reactions

Finally, the optimization of the Diels-Alder reaction^[24] was investigated (Table 4). Akai *et al.* previously examined 60 reaction conditions for optimization to obtain adduct **10** in 85% yield (60 W, 194 °C, 5 mL/min).^[21] In the case of the Diels-Alder reaction, when the reaction temperature exceeded 210 °C, the retro-Diels-Alder reaction occurred and the yield remarkably decreased. Thus, the first approximate surface became tubular (Figure 6-a). After eliminating the experimental points below the threshold, a three-dimensional surface could be created with a minimum number of 6 points (Figure 6-b). The 14th experiment was conducted according to the predicted optimum conditions (92 W, 3.4 mL/min), and **10** was obtained with 94% yield (entry 14). The productivity under this condition was 547 g/day (200 kg/year), which can be achieved with a single flow line.

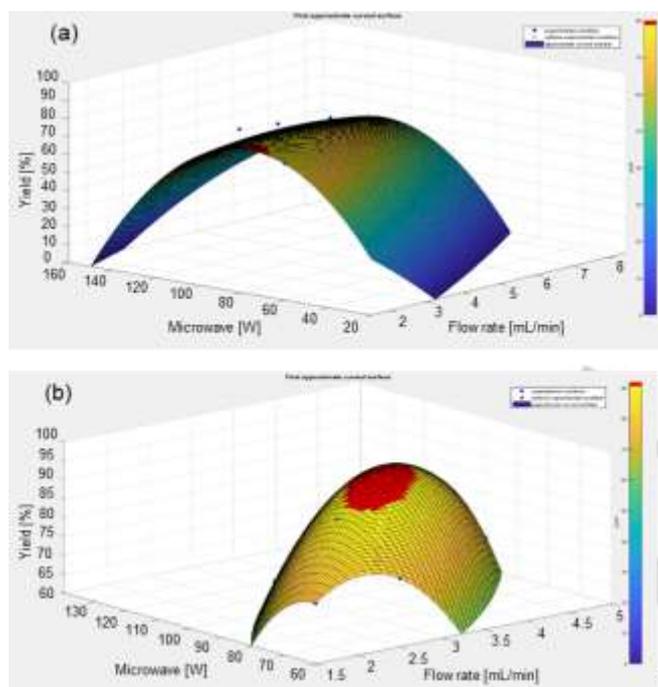
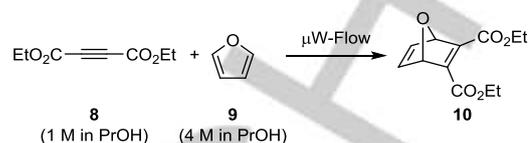


Figure 6. Three-dimensional surface approximation in Diels-Alder reactions: (a) Microwave Power-Flow rate-Yield; (b) Optimized Microwave Power-Flow rate-Yield.

Table 4. Results from the Diels-Alder reactions.



Entry	Microwave power [W]	Flow rate [mL/min] ^[a]	Temperature [°C] ^[b]	Yield [%] ^[c]
1 ^[d]	60	2.5 (145 s)	169	78
2	60	5 (73 s)	151	31
3	60	7.5 (48 s)	129	6
4	100	2.5 (145 s)	210	68
5	100	5 (73 s)	205	68
6	100	7.5 (48 s)	180	37
7	140	2.5 (145 s)	227	25
8	140	5 (73 s)	215	61
9	140	7.5 (48 s)	213	55
10	40	2.5 (145 s)	137	39
11	60	1.5 (240 s)	163	76
12	60	3.5 (103 s)	163	58
13	80	2.5 (145 s)	198	89
14	92	3.4 (107 s)	209	94

[a] Residence time in parentheses. [b] Outlet temperature. [c] Determined by ¹H NMR analysis using *p*-dimethoxyphenol as internal standard. [d] Best yield conditions.

3. Summary and Outlook

In this study, we developed a simple DoE method for optimization using a flow microwave system. The “9+4+1 method” for predicting optimized conditions was applicable to 7 of the 10 reactions investigated. In these cases, more than 99% of the

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conditions were predicted by the initial nine screenings, or adequate data for the optimization was not provided. The “9+4+1 method” can be easily applied for simple and quick two-factor optimization. Since the flow method can be easily scaled up compared with the conventional batch method, our approach would promote technology transfer from laboratory to industry for large-scale production of various fine and bulk chemicals. Optimizations related to other reactions will be reported elsewhere in due course.

Péter Vámosi was born in 1993 in Budapest, Hungary. He received his bachelor of science in 2016 at Budapest University of Technology and Economics in chemical engineering with specialization in pharmaceuticals. He continued his master studies at the same university. In 2017, he won the Suzuki Foundation's internship.



Kazuhiro Takeda was born in 1967 in Takamatsu, Japan. He received his Ph.D. degree from Kyushu University under the supervision of Prof. Matsuyama Hisayoshi in 1995. He began his academic career as an assistant professor at Kyushu University in the same year. He has been an associate professor of applied chemistry and biochemical engineering at the Graduate School of Engineering, Shizuoka University, since 2005. His current research interests are design optimization and automated operation of microwave flow reactors, business process model for safety operation, and kinetic analysis of conjugal transfer of plasmid.



Nobuyuki Mase was born in 1971 in Tokoname, Japan. He received his Ph.D. degree from Nagoya Institute of Technology under the supervision of Prof. Takeshi Toru in 1999. He began his academic career as an assistant professor at Shizuoka University in the same year. He joined Carlos F. Barbas, III group at The Scripps Research Institute as a visiting professor in 2003. He was an associate professor in materials science and chemical engineering at Shizuoka University from 2007 to 2013, and has been a professor of applied chemistry and biochemical engineering at the Graduate School of Engineering, Shizuoka University, since 2014. His current research interests are catalytic asymmetric synthesis with small organic molecules under environmentally friendly reaction conditions, development of organic synthetic methodology based on process and green chemistry, and fine bubble-based organic synthesis.



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Keywords: acylation • design of experiments • flow synthesis • microwave chemistry • optimization

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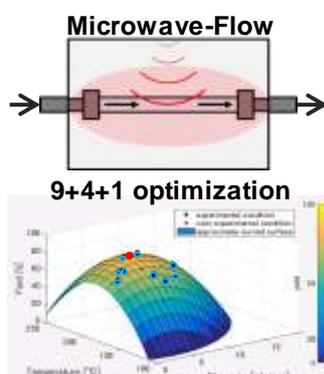
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PERSONAL ACCOUNT

A continuous flow microwave reactor has the potential for quick optimization of reaction conditions owing to the rapid uniform heating. In this study, we developed a “9+4+1 method” to optimize reaction conditions based on comprehensive reaction analysis using a flow microwave reactor. Our proposed method would facilitate industrial production of various fine and bulk chemicals without wastage and in a short time.



Péter Vámosi, Keiya Matsuo, Tsuguya Masuda, Kohei Sato, Tetsuo Narumi, Kazuhiro Takeda, and Nobuyuki Mase**

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Rapid Optimization of Reaction Conditions Based on Comprehensive Reaction Analysis Using a Continuous Flow Microwave Reactor