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An automated-flow microreactor system for quick optimization and production: application of 10- and 100-gram order productions of a matrix metalloproteinase inhibitor using a Sonogashira coupling reaction

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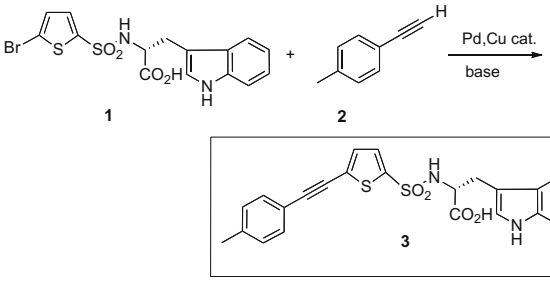
ABSTRACT

Sonogashira coupling reaction leading to a matrix metalloproteinase inhibitor was investigated using an automated microreactor system, which is a sequential temperature- and flow rate-programed reaction evaluation system. By repeating the use of this computer-controlled system four times, we were able to determine the optimal conditions and quickly apply them to a 10 g scale synthesis using the same microreactor system. The optimal conditions were also applied to a 100 g scale production by using another microflow system composed of a T-shaped micromixer (200 μm id) and a stainless tube reactor (2000 μm id and 20 m length). Total time spent for both optimization and production was as short as 50 h.

Microreaction systems have recently attracted attention in the field of organic synthesis.[1–3] In order to generalize microreaction technology and make it more chemist friendly, the development of a microreactor system that will allow speedy optimization of reaction conditions, such as flow rates and temperatures, is highly desirable because tedious and repetitious setup is generally required for each experiment of different microflow conditions. We have developed an automated PC-controlled microreactor system, which can accommodate the easy execution of multiple reaction conditions, such as flow rates and temperatures, with essentially a single setup.[4] Herein, we report that a Sonogashira reaction[5] leading to a matrix metalloproteinase inhibitor[6] can be quickly optimized using this automated microreactor system.[3a,7] We also report that the optimal conditions were immediately applied to a 100-g scale synthesis. Remarkably, the total time, including optimization and production, can be as little as 50 h.

Our group collaborated with Dainippon Screen Mfg. Co., Ltd, to develop an automated microreactor system that could be used to quickly identify optimal reaction conditions (Fig. 1). This microreactor system consists of a micromixer (1000 μm), a residence time unit (RTU, 1000 μm id and 10 m length), two pumps, and a fraction collector. Individual flow rates for solutions A and B, and temperatures of the micromixer and the RTU can be attired sequentially and automatically, based on the initial input from the software. The reaction mixture for each condition exiting the system is automatically sampled by a fraction collector. This system allows screening of up to 120 reaction conditions in one operation by programming temperatures and flow rates, and, therefore, the temperature and residence time can be quickly optimized (first stage, Scheme 1). The optimal conditions thus obtained can be applied to large-scale production using a robust microflow system (second stage).

The Sonogashira coupling reaction represents the cross-coupling of terminal alkynes and aryl halides leading to internal alkynes by the palladium catalyst, a copper co-catalyst, and a base.[5] The coupling reaction of bromothiophene derivative **1** and *p*-tolylacetylene (**2**) to obtain **3**, a matrix metalloproteinase inhivitor,[6] was settled upon as the model reaction for this work (Eq. 1).



(1)

For the initial screening of the Sonogashira reaction, seven conditions with different temperatures (70–110 °C) and residence times (20–60 min) were tested (Fig. 2). It was found that the optimal conditions (reaction temperature: 110 °C and residence time: 60 min) gave the desired coupling product in an 88% HPLC ratio (condition 7).[8] Although tolylacetylene (**2**) was totally consumed, a small amount of **1** remained due to the undesirable homocoupling of **2**.

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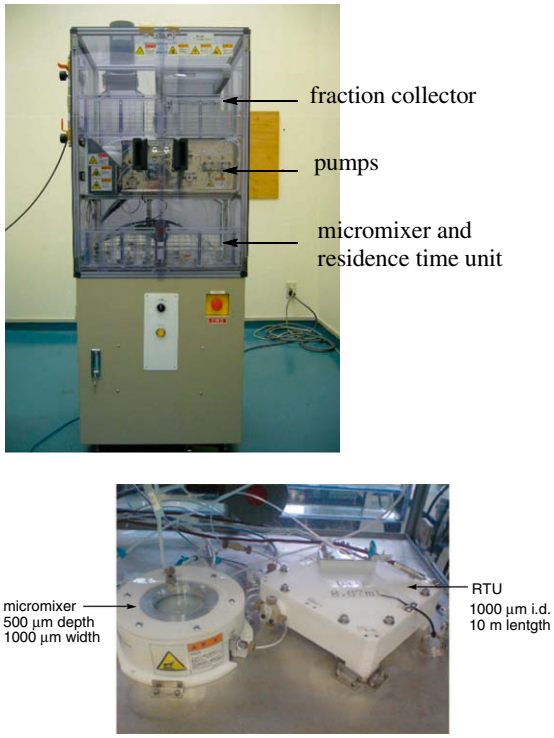
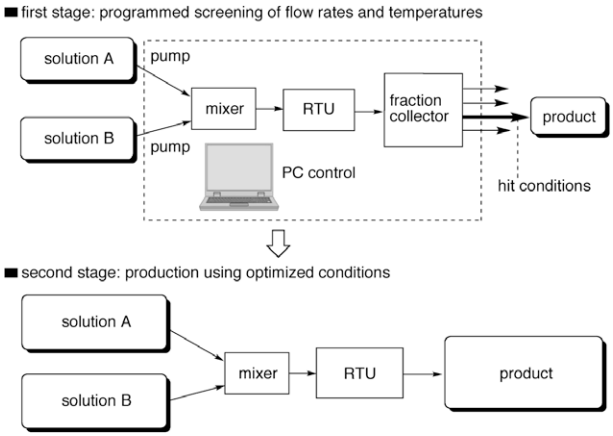


Figure 1. Pictures of the employed microreactor system (DSASS).



Scheme 1. Concept of the present model work.

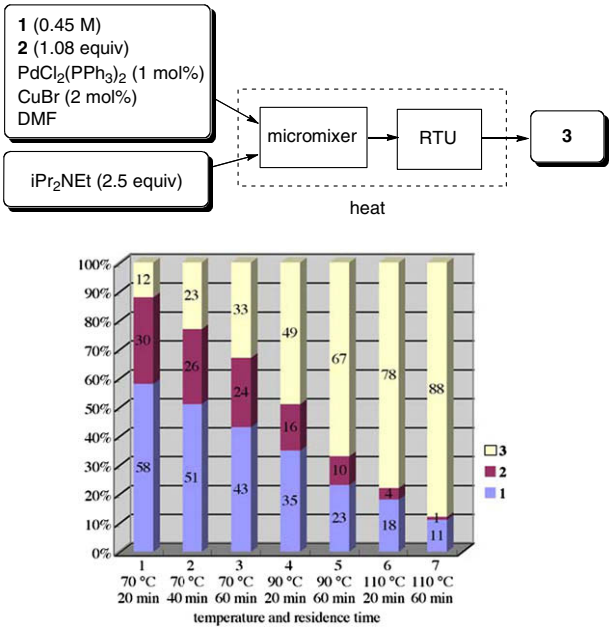


Figure 2. First screening, solution A: **1** (0.45 M in DMF), **2** (1.08 equiv), $PdCl_2(PPh_3)_2$ (1 mol %), CuBr (2 mol %), solution B: diisopropylethylamine (2.5 equiv).

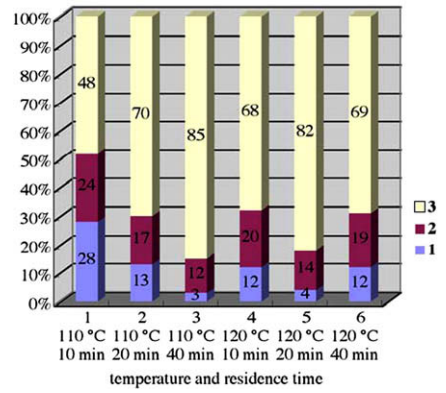


Figure 3. Second screening, solution A: **1** (0.45 M in DMF), tolylacetylene (1.3 equiv), $PdCl_2(PPh_3)_2$ (1 mol %), and CuBr (2 mol %), solution B: diisopropylethylamine (2.5 equiv).

Thus, a second set of experiments was carried out to improve the conversion of **1** using increased amounts of **2** (1.3 equiv) (Fig. 3). We examined another six conditions at 110 and 120 °C at varied residence times. The reaction at 110 °C with a 40 min residence time gave the desired product in good yield (condition 3). When the reaction was carried out at 120 °C under the same residence time, the pressure inside the microreactor rose gradually because of clogging, and the system was shut down for safety. The speculation was that the insoluble substances gradually accumulated inside the RTU and eventually clogged it. Gratifyingly, reaction with shorter residence time (20 min) could be carried out without any clogging. Therefore, we judged the reaction having the shorter residence time (condition 5) to be the best reaction condition for this screening. Although almost complete consumption of bromothiophene **1** was attained, the remaining tolylacetylene (**2**) posed a problem.

To investigate the optimal amount of *p*-tolylacetylene (**2**), reactions were carried out at 120 °C by adjusting the flow rates of solutions A and B. The results are shown in Figure 4. When 1.25 equiv of *p*-tolylacetylene was used, both **1** and **2** were almost consumed, whereas a small amount of **1** remained (condition 6). Similarly, we investigated the optimal amount of amine (Fig. 5), and found that when using 3 equiv of amine with a 20 min residence time, both **1** and **2** were almost consumed. Therefore, we adopted a condition 4 for gram-scale production. Continuous operation of the same system with no fraction collector was performed and **3** was obtained (8 h, 84% yield, 14 g of **3**) with no problems.

Although numbering up of microflow system allows large scale production, it is also important to increase the through put for one system. Encouraged by the above results, we next executed a 100-g scale production of **3** using a different robust microreactor system (Scheme 2), which was composed of pumps, a micromixer (MiChS type α micromixer,[9] 200 μm id) and a RTU (2 mm id and 20 m length). Temperature and residence time were set at 120 °C and 20 min. To realize high productivity, we used a RTU with a larger

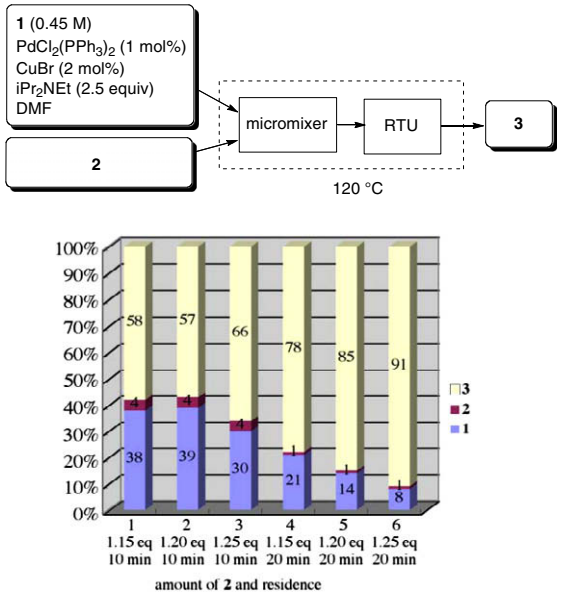


Figure 4. Third screening, solution A: **1** (0.45 M in DMF), $PdCl_2(PPh_3)_2$ (1 mol %), CuBr (2 mol %), diisopropylethylamine (2.5 equiv), solution B: **2**, reaction temperature: 120 °C.

internal volume that would allow for higher flow rates (total flow rate: 3.14 mL/min). When the system was continuously operated for 6 h, 113 g of **3** was obtained after recrystallization (70% yield).[10]

In conclusion, a Sonogashira coupling reaction leading to a matrix metalloproteinase inhibitor was investigated as a model reaction using the originally developed automated microflow system. Quick optimization of reaction conditions was accomplished and the application to a 10 g order synthesis with this system was achieved. Using the optimal conditions and a different robust microreactor system, we successfully carried out a 100-g scale production. The real and practical advantage of this system is manifested

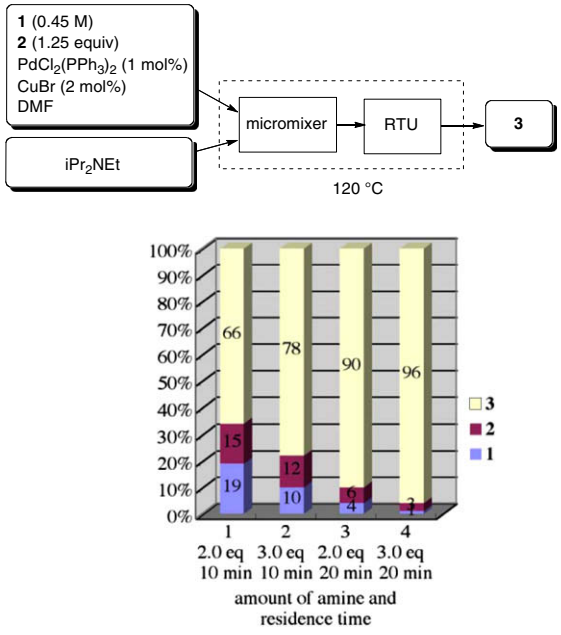
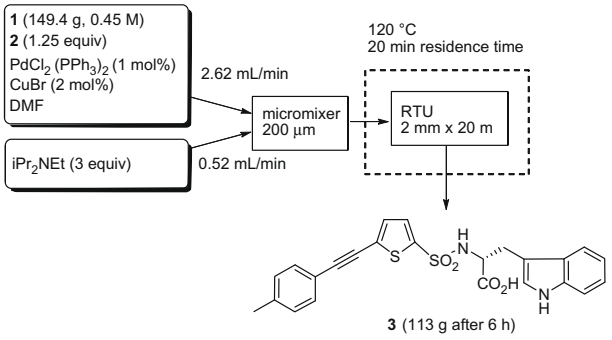


Figure 5. Fourth screening, solution A: **1** (0.45 M in DMF), $PdCl_2(PPh_3)_2$ (1 mol %), CuBr (2 mol %), and **2** (1.25 equiv), solution B: diisopropylethylamine, reaction temperature: 120 °C.



Scheme 2. 100-g scale production of **3**.

by its ability to eliminate the time lag between optimization and production as well as to shorten total processing time.

Acknowledgments

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References and notes

1. For selected reviews, see: (a) Ehrfeld, W.; Hessel, V.; Lowe, H. Microreactors: New Technology for Modern Chemistry; Wiley-VCH: Weinheim, 2000; (b) Wirth, T. Microreactors in Organic Synthesis and Catalysis; Wiley-VCH: Weinheim, 2008; (c) Yoshida, J.. *Flash Chemistry. Fast Organic Synthesis in Mirosystem*; Wiley: Chichester, 2008; (d) Hessel, V.; Renken, A.; Schouten, J. C.; Yoshida, J. *Micro Process Engineering*; Wiley-VCH: Weinheim, 2009; (e) Jahnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 406; (f) Geyer, K.; Codée, J. D. C.; Seeberger, P. H. *Chem. Eur. J.* **2006**, *12*, 8434; (g) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Asian J.* **2006**, *1*, 22; (h) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733; (i) Yoshida, J.; Nagaki, A.; Yamada, T. *Chem. Eur. J.* **2008**, *14*, 7450.
2. For an account of our work using microreactors, see: Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151.
3. For our recent work using microreactors, see: Sonogashira reaction: (a) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691; Mizoroki-Heck reaction: (b) Liu, S.; Fukuyama, T.; Sato, M.; Ryu, I. *Org. Process Res. Dev.* **2004**, *8*, 477; Carbonylative Sonogashira reaction: (c) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236; Photo-induced [2+2] cycloaddition: (d) Fukuyama, T.; Hino, Y.; Kamata, N.; Ryu, I. *Chem. Lett.* **2004**, *33*, 1430; Photo-induced Barton reaction: (e) Sugimoto, A.; Sumino, Y.; Takagi, M.; Fukuyama, T.; Ryu, I. *Tetrahedron Lett.* **2006**, *47*, 6197; (f) Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. *Tetrahedron* **2009**, *65*, 1593; Tin hydride mediated radical reaction: (g) Fukuyama, T.; Kobayashi, M.; Rahman, M. T.; Ryu, I. *Org. Lett.* **2008**, *10*, 533; Radical Carboaminoxylation: (h) Wienhöfer, I. C.; Studer, A.; Rahman, M. T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 2457; Radical carbonylation: (i) Fukuyama, T.; Rahman, M. T.; Kamata, N.; Ryu, I. *Beilstein. J. Org. Chem.* **2009**, *5*, 34.
4. For a catalyst-screening system using a microreactor, see: de Bellefin, C.; Tanchoux, N.; Caravieilhes, S.; Grenouillet, P.; Hessel, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3442.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467; For reviews, see: (b) Sonogashira, K.. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 521–549; (c) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 203–229; (d) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
6. Tamura, Y.; Watanabe, F.; Nakatani, T.; Yasui, K.; Fuji, M.; Komurasaki, T.; Tsuzuki, H.; Maekawa, R.; Yoshioka, T.; Kawada, K.; Sugita, K.; Ohtani, M. *J. Med. Chem.* **1998**, *41*, 640.
7. Sonogashira reaction in a microflow system Kawanami, H.; Matsushima, K.; Sato, M.; Ikushima, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5129.
8. Product ratio was determined by HPLC analysis by comparing the peak area with that of the standard solution containing an authentic sample. HPLC analysis was performed under the following conditions: column, Cosmosil 5C18-AR (4.6 × 150 mm); solvent, $MeCN/H_2O/AcOH$ (50/50/0.1); flow rate, 1 mL/min; detection, 254 nm. It takes ca. 20 min to analyze one sample.
9. Stainless steel made micormixer having T-shaped microchannel (200 µm id). see: http://www.michs.jp/.
10. Solution A (**1** (149.4 g, 0.45 M), **2** (50.5 g, 1.25 equiv), $PdCl_2(PPh_3)_2$ (2.44 g, 1 mol %) and CuBr (1.00 g, 2 mol %) in DMF (740 mL)) and solution B (diisopropylethylamine (134.9 g, 3.0 equiv)) were mixed in the micromixer (200 µm, flow rate; solution A: 2.62 mL/min, solution B: 0.52 mL/min), and

then the mixture was fed into the residence time unit (2 mm id, 20 m length, temperature: 120 °C, residence time: 20 min). After 6 h, ethyl acetate (500 mL) and 0.1 M hydrochloric acid (600 mL) were added to the reaction mixture. After phases were separated, methanol (150 mL) was added to the organic layer, and 10 wt % NaOH (260 mL) was dropped into the mixture to give a crystal. After the filtration, the crystal that was obtained was dissolved in water (480 mL) and ethyl acetate (1300 mL) was added. To this mixture was added concd HCl (60 g). The ethyl acetate layer was separated and the solvent was removed under reduced pressure. The crystal was dissolved in acetone (800 mL). Then, water (1200 mL) was dropped into the solution to give the crystal. The crystal was filtered and dried (113 g, 70% yield, mp = 180 °C, lit.[6] mp = 180–182 °C).