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Reductive Etherification under Microfluidic Conditions: Application to Practical Synthesis of the FGHIJ-Ring System of Yessotoxin

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Reductive etherification, a key reaction for constructing the H-ring in the convergent synthesis of the FGHIJ-ring system of yessotoxin, was problematic because the yield dramatically decreased upon increasing the scale of the reaction. This issue was solved by the use of a microflow reactor, and a gram scale reaction was successfully performed.

Reductive etherification is a key C–O bond forming reaction.[1] This method has been applied in natural product synthesis, e.g., the stereoselecive synthesis of the tetrahydropyran system of palytoxin by Kishi,[2] and the tetrahydrooxepin system of ladder-shaped polyethers by Nicolaou.[3] However, in other cases, no cyclization occurs under the reaction conditions to result in the formation of corresponding diols.[4] These problems can be overcome by reduction of the corresponding methyl acetals,[5,6] or mixed thioacetals derived via hydroxy dithioacetal cyclization.[7] Although there are limitations with reductive etherification, it is still a useful method for synthesizing ladder-shaped polyethers, because cyclic ethers can be synthesized in a straightforward manner from the corresponding hydroxy ketones or silyloxy ketones.[8]

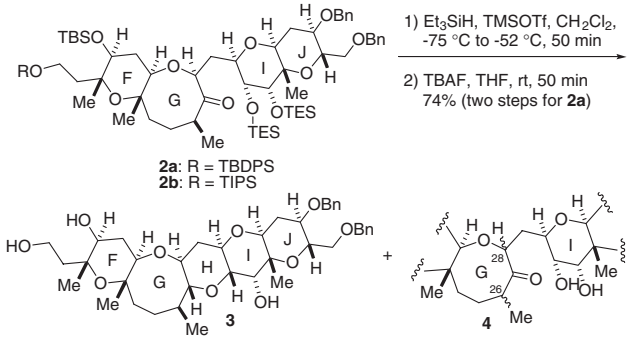
During the course of our synthetic studies of yessotoxin (YTX),[9] the FGHIJ-ring system of YTX was synthesized based on a convergent strategy via α-cyano ethers[10] in which the H-ring was constructed by reductive etherification (Scheme 1).[11] Treatment of hydroxy ketone **2a** with Et_3SiH/TMSOTf in CH_2Cl_2 at -75 to -52 °C, followed by removal of the silyl groups with TBAF, afforded the FGHIJ-ring unit **3** as a single isomer in 74% yield for two steps. However, the reductive etherification step became problematic when the reaction was scaled up (Table 1). Although the reaction using 20 mg of **2a** was reproducible to give **3** in 81% yield (Entry 1), the yield using 121 mg of **2a** dramatically dropped to 19% with concomitant formation of hydroxy ketone **4** as a mixture of diastereomers in 73% yield (Entry 2). When $BF_3 \cdot OEt_2$ was used as a Lewis acid (Entries 3 and 4), the yield of **3** also decreased when the amount of the substrate **2a** was increased. Attempts to improve the yield of **3** failed irrespective of considerable experimentation under various conditions, e.g., reaction temperature, addition rate of reagents, and reverse addition of the substrate to the reagents.

Table 1. Reductive etherification under batch and microfluidic conditions[15]

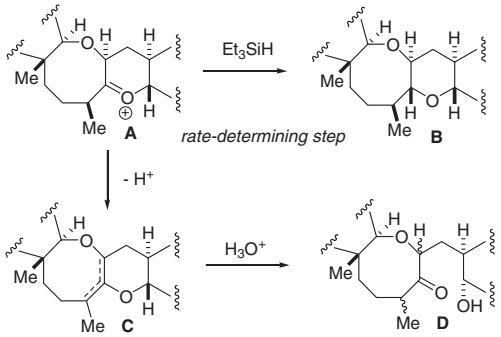
Entry	Substrate[a]	Lewis acid	Temp/°C	Yield of **3**/%[d]
1[b]	**2a** (20)	TMSOTf	−78 to −50	81
2[b]	**2a** (121)	TMSOTf	−78 to −50	19 (73)[e]
3[b]	**2a** (26)	$BF_3 \cdot OEt_2$	−50 to −18	86
4[b]	**2a** (135)	$BF_3 \cdot OEt_2$	−50 to −18	47 (41)[e]
5[c]	**2b** (138)	TMSOTf	−30	82
6[c]	**2a** (405)	TMSOTf	−30	81
7[c]	**2b** (1523)	TMSOTf	−30	86

[a]The numbers in parentheses represent the weights (mg) of the substrate **2**. [b]Method A: The reaction was carried out in a flask (batch). [c]Method B: The reaction was carried out under microfluidic conditions. [d]Yields in two steps after removal of silyl groups. [e]Yields in parentheses are for by-product **4**.

Possible reaction pathways of the reductive etherification are shown in Scheme 2. By the action of TMSOTf, the ketone **2** is converted to oxocarbenium ion **A**. Nucleophilic attack of the hydride (Et_3SiH) giving desired product **B** is considered to be the rate-determining step. When the hydride attack is slow, deprotonation from **A** occurs to form enol ether **C**, which is hydrolyzed to give the hydroxy ketones **D** as by-products. Therefore, the challenge is to accelerate the rate of hydride attack. One of the possible measures might be to increase the concentration of the reagents, and to mix the substrate and reagents expeditiously. However, optimization of reaction conditions using a large amount of sample is a high-risk experiment. Therefore, we planned to carry out the reaction under microfluidic conditions.



Scheme 1.



Scheme 2.

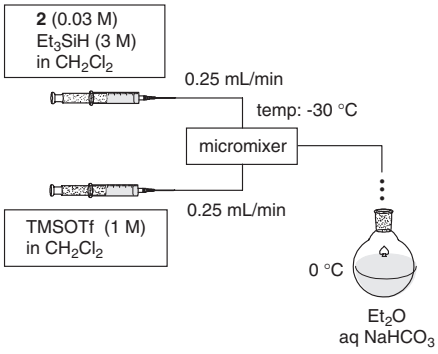


Figure 1. Schematic drawing of the reaction system under microfluidic conditions.

Microflow reactor is a powerful tool in modern organic synthesis.[12–14] Comet X-01® (Techno applications) was used for the reductive etherification. A solution of **2** (0.03 M) and Et_3SiH (3 M) in CH_2Cl_2 and a solution of TMSOTf (1 M) in CH_2Cl_2 were charged in gas-tight syringes, which were connected to the microflow reactor (Figure 1). After optimization of the reaction conditions, the solutions were transmitted using a syringe pump at a rate of 0.25 mL min^{-1} while cooling the reactor at −30 °C. The solutions were mixed vigorously by passing them through ca. 50-μL volume of the reactor with effective heat exchange to maintain the temperature precisely, and the resulting mixture was poured into aqueous $NaHCO_3$ at 0 °C. After extraction with Et_2O, the crude product was treated with TBAF in THF to afford triol **3**. As shown in Entry 5 (Table 1), when 138 mg of **2b** was subjected to reductive etherification under microfluidic conditions, an 82% yield of **3** was obtained, and the results were comparable to those of the small scale reaction (Entries 1 and 3). Clearly, the results were not affected by the reaction scale, because the solutions were continuously mixed into the reactor without change in the concentration gradient. When 405 mg of **2a** (Entry 6) and ca. 1.5 g of **2b** (Entry 7) were used, 81% and 86% yields of **3** were obtained, respectively. Thus, the utilization of microflow reactors is particularly effective for precious substrates obtained after multistep syntheses, because once the reaction conditions are optimized on a small scale, the bulk of the reaction solution can be increased infinitely in principle.

In conclusion, utilization of a microflow reactor is effective for reductive etherification in the practical synthesis of the FGHIJ-ring system of yessotoxin. Studies on the scope and limitation of the present technique to polyether synthesis are in progress in our laboratory.

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References and Notes

1 M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1987**, *52*, 4314.
2 M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976.
3 K. C. Nicolaou, C.-K. Hwang, D. A. Nugiel, *J. Am. Chem. Soc.* **1989**, *111*, 4136.
4 K. C. Nicolaou, C.-K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. B. Reddy, S. A. DeFrees, D. R. Reddy, R. A. Awartani, *J. Am. Chem. Soc.* **1995**, *117*, 10227.
5 T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett.* **1979**, *20*, 4679.
6 a) T. Oishi, Y. Nagumo, M. Shoji, J.-Y. Le Brazidec, H. Uehara, M. Hirama, *Chem. Commun.* **1999**, 2035. b) T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 3599. c) M. T. Crimmins, P. J. McDougall, K. A. Emmitte, *Org. Lett.* **2005**, *7*, 4033.
7 K. C. Nicolaou, M. E. Duggan, C.-K. Hwang, *J. Am. Chem. Soc.* **1986**, *108*, 2468.
8 S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, M. Nishizawa, *Tetrahedron Lett.* **1994**, *35*, 4367.
9 a) K. Watanabe, M. Suzuki, M. Murata, T. Oishi, *Tetrahedron Lett.* **2005**, *46*, 3991. b) T. Oishi, M. Suzuki, K. Watanabe, M. Murata, *Heterocycles* **2006**, *69*, 91. c) T. Oishi, M. Suzuki, K. Watanabe, M. Murata, *Tetrahedron Lett.* **2006**, *47*, 3975. d) K. Watanabe, H. Minato, M. Murata, T. Oishi, *Heterocycles* **2007**, *72*, 207.
10 T. Oishi, K. Watanabe, M. Murata, *Tetrahedron Lett.* **2003**, *44*, 7315.
11 K. Torikai, K. Watanabe, H. Minato, T. Imaizumi, M. Murata, T. Oishi, *Synlett* **2008**, 2368.
12 a) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**. b) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering*, Wiely-VCH Verlag, Weinheim, **2004**. c) J. Yoshida, *Flash Chemistry. Fast Organic Synthesis in Microsystems*, Wiley-Blackwell, **2008**.
13 Reviews for microreactor: a) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem., Int. Ed.* **2004**, *43*, 406. b) P. Watts, S. J. Haswell, *Chem. Soc. Rev.* **2005**, *34*, 235. c) K. Geyer, J. D. C. Codée, P. H. Seeberger, *Chem.—Eur. J.* **2006**, *12*, 8434. d) A. J. deMello, *Nature* **2006**, *442*, 394. e) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1*, 22. f) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300. g) B. Ahmed-Omer, J. C. Brandt, T. Wirth, *Org. Biomol. Chem.* **2007**, *5*, 733. h) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151. i) J. Yoshida, A. Nagaki, T. Yamada, *Chem.—Eur. J.* **2008**, *14*, 7450.
14 Some recent examples: a) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666. b) K. Fukase, M. Takashina, Y. Hori, D. Tanaka, K. Tanaka, S. Kusumoto, *Synlett* **2005**, 2342. c) P. He, P. Watts, F. Marken, S. Haswell, *Angew. Chem., Int. Ed.* **2006**, *45*, 4146. d) Y. Uozumi, Y. Yamada, T. Beppu, N. Fukuyama, M. Ueno, T. Kitamori, *J. Am. Chem. Soc.* **2006**, *128*, 15994. e) O. Flögel, J. D. C. Codée, D. Seebach, P. H. Seeberger, *Angew. Chem., Int. Ed.* **2006**, *45*, 7000. f) K. Tanaka, S. Motomatsu, K. Koyama, S. Tanaka, K. Fukase, *Org. Lett.* **2007**, *9*, 299. g) C. H. Hornung, M. R. Mackley, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2007**, *11*, 399. h) K. Tanaka, K. Fukase, *Synlett* **2007**, 164. i) T. Fukuyama, M. Kobayashi, M. T. Rahman, N. Kamata, I. Ryu, *Org. Lett.* **2008**, *10*, 533. j) A. Nagaki, Y. Tomida, J. Yoshida, *Macromolecules* **2008**, *41*, 6322. k) A. Nagaki, E. Takizawa, J. Yoshida, *J. Am. Chem. Soc.* **2009**, *131*, 1654. l) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Lett.* **2009**, *38*, 486.
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