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Microreactors

Room-Temperature Swern Oxidations by Using a Microscale Flow System**

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Microreactors (microstructured chemical reactors)[1] are expected to make a revolutionary change in chemical synthesis[2] from both the academic and industrial viewpoints.[3] Microreactors exhibit numerous practical advantages, including safety, easy modulation, and easy scale-up for industrial production, when compared with conventional macroscale batch reactors.[4] It is also advantageous that highly exothermic reactions can be conducted on the basis of efficient mass and heat transfer.[5] Microreactors also enable the precise control of reactive intermediates and thereby facilitate highly selective reactions that are difficult to achieve in conventional reactors.[6] Herein, we report that the Swern oxidation can be accomplished by using a microreactor at temperatures between −20 and 20 °C, much higher temperatures than those required for conventional macroscale batch reactors (−50 °C or below).

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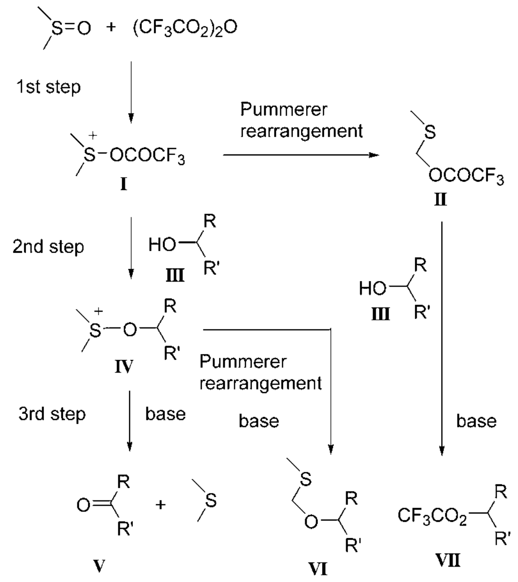
The oxidation with dimethyl sulfoxide (DMSO), known as the Moffatt–Swern type oxidation, is one of the most versatile and reliable methods for the oxidation of alcohols into carbonyl compounds and is widely utilized in organic synthesis.[7] Various methods for the activation of DMSO have been developed so far, and activation with trifluoroacetic anhydride (TFAA) is frequently employed in modern organic synthesis.[8] It is well known that activation of DMSO leads to an inevitable side reaction, the Pummerer rearrangement. Therefore, the reaction is usually carried out at low temperatures (−50 °C or below) at which the side reaction is very slow. However, the requirement for such low temperatures causes severe limitations in the industrial use of this highly useful reaction.

The Swern oxidation with TFAA generally proceeds as depicted in Scheme 1. In the first step, DMSO (usually in excess) reacts with TFAA to form cationic intermediate **I**, which is known to be stable only below −30 °C.[9] Therefore, the first step is usually carried out below −50 °C. At higher temperatures, the rearrangement of **I** takes place to give **II**. Therefore, **I** is immediately allowed to react with an alcohol **III** at or below −50 °C to obtain intermediate **IV** (the second step).



Scheme 1. The proposed mechanism of the Swern oxidation with TFAA.

In the third step, **IV** is treated with a base (usually triethylamine) to obtain the corresponding carbonyl compound **V** and dimethyl sulfide. However, upon treatment with a base, **IV** may also undergo the Pummerer rearrangement to give a methylthiomethyl ether (MTM ether) **VI**. Another important byproduct is the trifluoroacetate (TFA ester) **VII**, which is formed by the reaction of **II** with an alcohol **III** upon treatment with a base. In fact, the reaction of DMSO with TFAA at or above −30 °C mainly led to the formation the Pummerer rearrangement product **II**, and a significant amount of **VII** is therefore eventually formed in the final stage.

We examined the Swern oxidation by using a microscale flow system consisting of multilamination-type micromixers[10] and stainless tube reactors, as represented in Figure 1. A solution of DMSO (4.0 M) in CH$_2$Cl$_2$ (flow rate: 1 mL min^{-1}, 4 mmol min^{-1}) and a solution of TFAA (2.4 M) in CH$_2$Cl$_2$ (flow rate: 1 mL min^{-1}, 2.4 mmol min^{-1}) were introduced to the first micromixer (M1) by using syringe pumps.[11] The resulting solution was passed through reactor R1 and was mixed with a solution of the alcohol (1.0 M) in CH$_2$Cl$_2$ (flow rate: 2 mL min^{-1}, 2 mmol min^{-1}) in the second micromixer (M2). The resulting solution was passed through reactor R2 and was mixed with a solution of triethylamine (1.45 M) in CH$_2$Cl$_2$ (flow rate 4 mL min^{-1}, 5.8 mmol min^{-1}) in the third micromixer (M3). The solution was then introduced to tube reactor R3 before being passed through reactor R4. The three mixers (M1–3) and three of the reactors (R1–R3) were dipped in a cooling bath. Reactor R4 was dipped in a bath maintained at 30 °C. The outlet solution was collected and was analyzed by GC with an internal standard. The residence time in each reactor was as follows: R1: 0.01–2.4 s, R2: 1.2 s, R3: 1.2 s, R4: 5.9 s. After a steady state was reached, an aliquot of the product solution was taken over a period of 1.0 min and analyzed by GC.

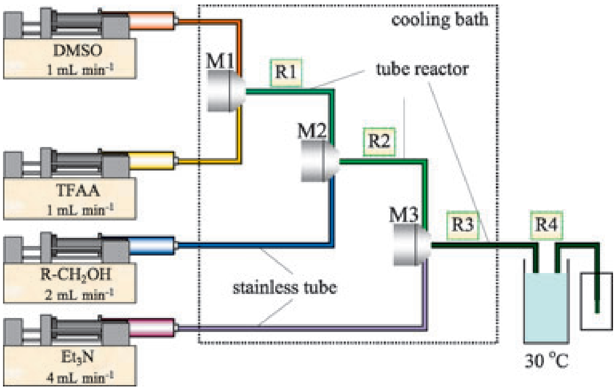


Figure 1. Schematic diagram of the microscale flow system for the Swern oxidation.

As indicated in Table 1, the oxidation of primary, secondary, cyclic, and benzylic alcohols took place smoothly to give the corresponding carbonyl compounds in good yields and with good selectivity at −20 °C (R1: 2.4 s). It is noteworthy that the reactions with a conventional macroscale batch reactor (a 30 mL flask with magnetic stirring) at the same temperature led to the formation of significant amounts of trifluoroacetates **VII** and the yields of the carbonyl compounds **V** were low. Significant amounts of substrate alcohols **III** also remained unchanged in the macroscale batch system. The dramatic effect of the microscale flow system seems to be attributable to precise temperature control (small local deviation of temperature in the reactor) and extremely fast and efficient mixing by virtue of a short diffusion path in the micromixer. Short residence time also seems to play a crucial role because fast transfer of the reactive intermediate to the next reactor seems to be essential for the present transformation.

Table 1: Swern oxidation of alcohols by using the microscale flow system and macroscale batch system.[a]

Alcohol **III**	System	Residence time in R1 [s]	*T* [°C]	Conversion [%]	Yield of **V** [%]	Yield of **VI** [%]	Yield of **VII** [%]
1-decanol	microscale flow	2.4	−20	95	75	8	19
		0.01	0	94	70	6	22
		0.01	20	96	71	6	22
	macroscale batch		−20	73	11	1	90
2-octanol	microscale flow	2.4	−20	92	95	5	2
		0.01	0	91	86	4	3
		0.01	20	88	89	3	2
	macroscale batch		−20	51	20	2	75
cyclohexanol	microscale flow	2.4	−20	88	88	6	5
		0.01	0	90	89	7	1
		0.01	20	81	88	5	2
	macroscale batch		−20	86	19	2	70
			−70	88	83	10	5
benzyl alcohol	microscale flow	2.4	−20	97	91	n.d.[b]	8
		0.01	0	100	78	n.d.[b]	14
		0.01	20	100	75	n.d.[b]	16
	macroscale batch		−20	80	49	n.d.[b]	50

[a] Yields were determined by GC withan internal standard and are based upon the amount of the alcohol consumed. [b] n.d. = not determined.

The success of the Swern oxidation by using the microscale flow system at −20 °C prompted us to examine further increases in the reaction temperature. The reaction at 0 °C resulted in a significant decrease in the yield of carbonyl compounds **V** (32 % for cyclohexanol; results not shown). Presumably Pummerer rearrangement of intermediate **I** took place to give **II** at this temperature. However, we found that by shortening the residence time (R1: 0.01 s) the desired carbonyl compounds **V** were obtained in good yields even at 0 °C. More outstanding is the fact that the reaction can be conducted even at room temperature (20 °C) to obtain **V** in good yields. This success of the Swern oxidation at room temperature seems to be attributable to the extremely short residence time, which ensures very fast transfer of the highly unstable intermediate **I** to the next reactor before decomposition.

It is important to check the durability of the process for scale-up. So, we ran the reaction of cyclohexanol for 3 h (0.36 mol scale) at 20 °C and found that the alcohol conversion and product selectivity did not change (Table 2). Another important point is that microsystems serve as a quick means for scale-up, because the quality of the product does not change during the course of scale-up, although batch methods suffer from such a problem.

Table 2: Continuous Swern oxidation of cyclohexanol by using the microscale flow system at 20 °C.[a]

t [h]	Conversion [%]	Yield of **V** [%]	Yield of **VI** [%]	Yield of **VII** [%]
0	83	92	5	4
0.5	84	92	5	4
1.0	85	89	5	4
1.5	81	89	4	4
2.0	86	91	5	3
2.5	87	91	5	3
3.0	85	91	5	4

[a] Yields were determined by GC with an internal standard and are based upon the amount of the alcohol consumed.

In conclusion, the present observations demonstrate a striking example of the effectiveness of the microscale flow system for a reaction involving highly unstable intermediates. Further improvement of the reaction system and applications to the synthesis of various carbonyl compounds are in progress.

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Keywords: alcohols · microreactors · oxidation · Swern oxidation · synthetic methods

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[1] a) *Microreaction Technology* (Ed.: W. Ehrfeld), Springer, Berlin, **1998**; b) W. Ehrfeld, V. Hessel, H. Löwe, *Microreactors*, Wiley-VCH, Weinheim, **2000**; c) *Microsystem Technology in Chemistry and Life Sciences* (Eds.: A. Manz, H. Becker), Springer, Berlin, **1999**; d) V. Hessel, S. Hardt, H. Löwe, *Chemical Micro Process Engineering*, Wiley-VCH, Weinheim, **2004**.

[2] a) H. Salimi-Moosavi, T. Tang, D. J. Harrison, *J. Am. Chem. Soc.* **1997**, *119*, 8716–8717; b) C. de Bellefon, N. Tanchoux, S. Caravieilhes, P. Grenouillet, V. Hessel, *Angew. Chem.* **2000**, *112*, 3584–3587; *Angew. Chem. Int. Ed.* **2000**, *39*, 3442–3445; c) H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara, T. Kitamori, *Chem. Commun.* **2001**, 2662–2663; d) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Chem. Commun.* **2002**, 1034–1035; e) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, *4*, 1691–1694; f) E. Garcia-Egido, V. Spikmans, S. Y. F. Wong, B. H. Warrington, *Lab Chip* **2003**, *3*, 73–76; g) M. Ueno, H. Hisamoto, T. Kitamori, S. Kobayashi, *Chem. Commun.* **2003**, 936–937; h) S. M. Lai, R. Martin-Aranda, K. L. Yeung, *Chem. Commun.* **2003**, 218–219; i) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305–1308; j) T. Wu, Y. Mei, J. T. Cabral, C. Xu, K. L. Beers, *J. Am. Chem. Soc.* **2004**, *126*, 9880–9881.

[3] Example reviews: a) S. H. DeWitt, *Curr. Opin. Chem. Biol.* **1999**, *3*, 350–356; b) H. Okamoto, *J. Syn. Org. Chem. Jpn.* **1999**, *57*, 805–812; c) T. Sugawara, *Pharmacia* **2000**, *36*, 34–38; d) O. Wörz, K. P. Jäckel, T. Richter, A. Wolf, *Chem. Eng. Sci.* **2001**, *56*, 1029–1033; e) S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts, P. Styring, *Chem. Commun.* **2001**, 391–398; f) K. F. Jensen, *Chem. Eng. Sci.* **2001**, *56*, 293–303; g) A. de Mello, R. Wootton, *Lab Chip* **2002**, *2*, 7N–13N; h) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem.* **2004**, *116*, 410–451; *Angew. Chem. Int. Ed.* **2004**, *43*, 406–446. .

[4] S. Taghavi-Moghadam, A. Kleemann, K. G. Golbig, *Org. Process Res. Dev.* **2001**, *5*, 652–658.

[5] a) R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883–884; b) M. T. Janicke, H. Kestenbaum, U. Hagendorf, F. Schüth, M. Fichtner, K. Schubert, *J. Catal.* **2000**, *191*, 282–293; c) M. W.

Losey, M. A. Schmidt, K. F. Jensen, *Ind. Eng. Chem. Res.* **2001**, *40*, 2555–2562.

[6] For example, a) S. Suga, M. Okajima, K. Fujiwara, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 7941–7942; b) J. Yoshida, S. Suga, *Chem. Eur. J.* **2002**, *8*, 2651–2658; c) S. Suga, A. Nagaki, J. Yoshida, *Chem. Commun.* **2003**, 354–355; d) S. Suga, A. Nagaki, Y. Tsutsui, J. Yoshida, *Org. Lett.* **2003**, *5*, 945–947; e) A. Nagaki, K. Kawamura, S. Suga, T. Ando, M. Sawamoto, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 14702–14703.

[7] For example, T. T. Tidwell, *Org. React.* **1990**, *39*, 297–572.

[8] a) K. Omura, A. K. Sharma, D. Swern, *J. Org. Chem.* **1976**, *41*, 957–962; b) K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651–1660.

[9] a) A. K. Sharma, D. Swern, *Tetrahedron Lett.* **1974**, 1503–1506; b) A. K. Sharma, T. Ku, A. D. Dawson, D. Swern, *J. Org. Chem.* **1975**, *40*, 2758–2764.

[10] The IMM (Institut für Mikrotechnik Mainz GmbH) single mixer, version 2, (http://www.imm-mainz.de/) was used. The inlay is made of silver and the channel width is 40 μm.

[11] The Harvard PHD2000 Programmable syringe pump, Harvard Pump11 (http://www.harvardapparatus.com/), and kdScientific model 100 syringe pump (http://www.kdscientific.com/) were used.