COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Phase-transfer alkylation reactions using microreactors

Masaharu Ueno,[a] Hideaki Hisamoto,[b] Takehiko Kitamori[b] and Shū Kobayashi*[a]

[a] *Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan. E-mail: skobayas@mol.f.u-tokyo.ac.jp; Fax: +81 3 5684 0634; Tel: +81 3 5841 4790*

[b] *Department of Applied Chemistry, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8656, Japan*

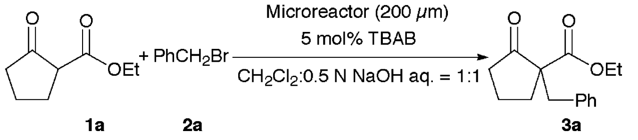
Received (in Cambridge, UK) 12th February 2003, Accepted 5th March 2003
First published as an Advance Article on the web 27th March 2003

Phase-transfer alkylation in a microreactor proceeds smoothly, and the reaction has been found to be more efficient than that in a round-bottomed flask with vigorous stirring; we have observed by an optical microscope study that an interfacial area provided by organic and aqueous phases is more extended in a microreactor.

Recent microchip technology has enabled versatile applications in chemistry. In particular, applications in the field of analytical chemistry have been established as one of the promising research fields.[1] On the other hand, increasing interest has also been paid to applications in synthetic organic chemistry.[2–7] A liquid microspace such as a microchannel on a glass microchip provides interesting characteristics such as short molecular diffusion distance, large specific interfacial area, and small heat capacity, all of which would be expected to promote highly effective chemical reactions in the microchip.

When organic and aqueous phases are introduced through two inlets of a microchannel, a large specific interfacial area would be obtained without any stirring. By utilizing the large specific interfacial area provided by organic and aqueous phases, it is expected that efficient phase transfer processes can be performed with high yields.[8] Based on this idea, we planned to perform several fundamental carbon–carbon bond-forming reactions in microreactors. In this paper, we report phase-transfer alkylation reactions of β-keto esters in microreactors.

Alkylation reactions of β-keto esters are among the most important carbon–carbon bond-forming reactions in organic synthesis.[9–11] First, we tested the benzylation reaction of ethyl 2-oxocyclopentanecarboxylate **(1a)** with benzyl bromide **(2a)** in the presence of 5 mol % of tetrabutylammoniun bromide (TBAB) as a phase transfer catalyst (Scheme 1). The experiment system of a microreactor is illustrated in Fig. 1. A teflon tube (ø200 µm × 10 cm) was connected at the end of the microchip (the channels were 200 µm in width, 100 µm in depth, and 45 cm in length) and the calculated total volume of the microchannel contained the volume of the tube. The reaction was performed by introducing a dichloromethane solution containing **1a** (0.30 M), **2a** (0.45 M), and resorcinol dimethyl ether as an internal standard, and an aqueous solution containing sodium hydroxide (0.50 N) and TBAB (0.015 M) through the two-inlets of the microchip under continuous flow conditions at ambient temperature. Mean residence time of the starting materials in the microreactor was determined by total volume of the microchannel and volume flow rates of the organic and aqueous phases. Yields were determined by collecting the definite volume of the product from the output of the microreactor, while the flow rate was kept constant. We measured yields of the product at several points of mean residence time by HPLC analysis.



Scheme 1 The phase-transfer benzylation reaction of ethyl 2-oxocyclopentanecarboxylate (**1a**) with benzyl bromide (**2a**).

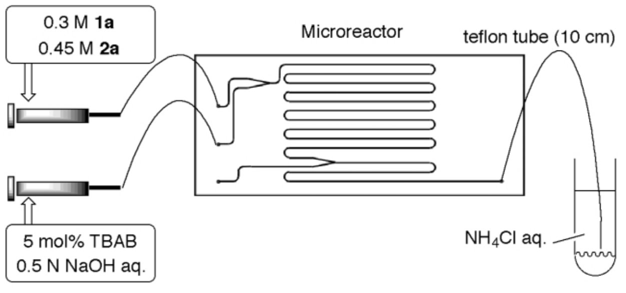


Fig. 1 An experiment system of a microreactor.

The profile of the alkylation of **1a** with **2a** in the microreactor is shown in Fig. 2 (a). The reaction proceeded smoothly, and the desired alkylation product **3a** was obtained in 57% yield in the microreactor at 60 seconds. The yield increased to over 90% after 300 seconds. We also conducted macroscale experiments using normal batch systems for comparison. In the cases of the macroscale reactions, 2.0 ml each of the reagent solutions was poured into a round-bottomed flask and stirred. Reaction rates of the benzylation were dependent on the stirring conditions (Fig. 2). Product **3a** was obtained in 37% yield after vigorous stirring (1350 rpm) for 60 seconds, while lower yields of the product were obtained with slower stirring rate (400 rpm) or without stirring. It is noted that a much higher yield was obtained using a microreactor than that using standard batch systems even with vigorous stirring. In this phase-transfer benzylation, larger interfacial areas are expected to increase yields of the product, and it has been demonstrated that the microreactor system is superior to normal batch systems to create such reaction conditions.

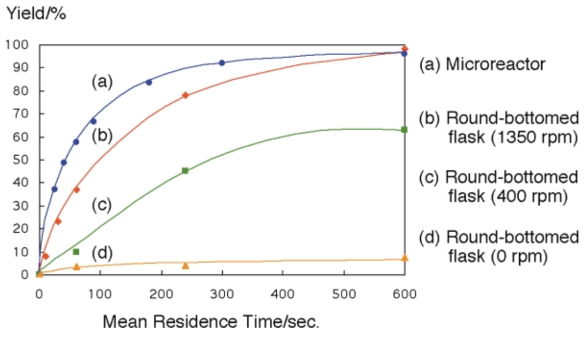


Fig. 2 The profile of the alkylation of **1a** with **2a** in a microreactor and standard batch systems.

Next, we examined the effect of the width of the microchannels for reactors (Fig. 3). In microchip reactors with thinner channel width, higher reaction rates of the benzylation were observed. In all cases shown in Fig. 3, segment states, which were formed by continuous flow of organic and aqueous layers in the microchannel, were observed. These results suggested that smaller particles formed by the thinner channel width in the microreactors provided larger interfacial area. The shape of the segment using an optical microscope is shown in Fig. 4.[12] It was

DOI: 10.1039/b301638b

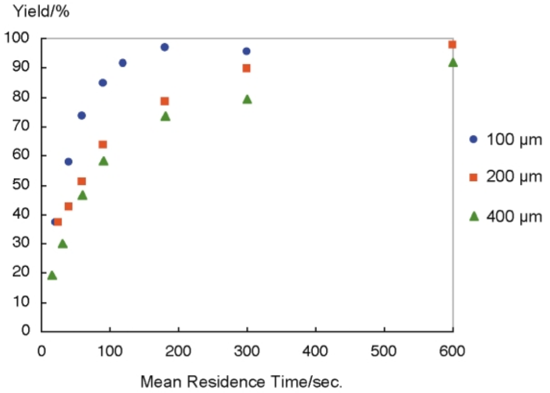


Fig. 3 The effect of the width of the reactors.

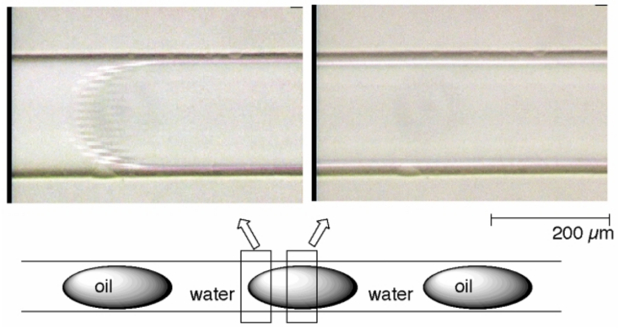


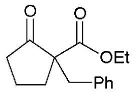
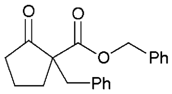
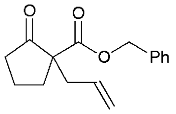
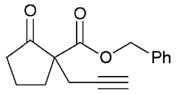
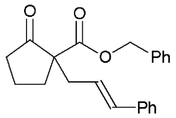
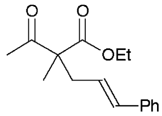
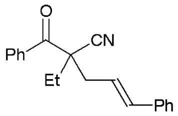
Fig. 4 The shape of the segment (optical microscope). The length of the segment is *ca*. two to five times of the channel width.

shown that the organic phases were divided into small droplets and flowed inside the aqueous tube. These segments were formed presumably due to the difference in affinity of the organic and aqueous layers with the glass wall of the microchannels. It is noteworthy that a larger interfacial area was formed not only in both ends of the segments but also around the organic droplets.

We examined phase-transfer alkylation reactions using several other substrates in a microchip reactor (Table 1). Under the microscale conditions, the flow rate was kept constant for the mean residence time of 2 or 10 min (5.9 μl min^{-1} for 2 min and 1.2 μl min^{-1} for 10 min), and the yield was determined by collecting 0.2 mmol of the substrates (0.67 ml of 0.3 M solution) and isolation by the usual methods. In all cases, the reactions proceeded smoothly to afford the desired alkylated adducts in high yields. As comparison, we performed macroscale reactions; the same volume of organic and aqueous layers (0.67 ml each) was mixed under vigorous stirring, and after 2 min, the reaction mixture was quenched with aqueous saturated ammonium chloride, and the product was isolated by the usual methods. In the reactions using not only benzyl bromide but also various alkyl bromides as alkylation reagents, and an α-cyano ketone[13] as a substrate, the phase-transfer alkylation in microreactor gave higher yields than those in a round-bottomed flask with vigorous stirring at the same residence time.

In conclusion, we have revealed that phase-transfer alkylation in a microchip reactor was more reactive than that in a round-bottomed flask with vigorous stirring. To the best of our knowledge, this is the first example of synthetically useful phase-transfer carbon–carbon bond-forming reactions in a microchip reactor. By optical microscope study, we observed that the interfacial area provided by organic and aqueous phases was more extended in the microchannel for reactors. Further investigation to develop other synthetic reactions in a microchip reactor is now in progress.

Table 1 Phase-transfer alkylation of other substrates[a]

Product	2 min	10 min
	75% (49%)	96%
	73% (48%)	85%
	45% (18%)	87%
	35% (18%)	92%
	91% (87%)	97%
	65% (20%)	71%
	44% (17%)	90%

[a] Isolate yield. In the parentheses, macroscale reactions for 2 min. See text.

This work was partially supported a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science.

Notes and references

1 W. Ehrfeld, V. Hessel and H. Löwe, in *Microreactors*, Wiley-VCH, Weinheim, 2000.
2 S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts and P. Styring, *Chem. Commun.*, 2001, 391.
3 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. Zhang, *Tetrahedron*, 2002, 4735.
4 C. Bellefon, N. Tanchoux, S. Caravieilhes, P. Grenouillet and V. Hessel, *Angew. Chem., Int. Ed*, 2000, **39**, 3442.
5 S. Suga, M. Okajima, K. Fujiwara and J-i. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 7941; J-i. Yoshida and S. Suga, *Chem. Eur. J*, 2002, **8**, 2650.
6 T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691.
7 M. Tokeshi, T. Minagawa, K. Uchiyama, A. Hibara, K. Sato, H. Hisamoto and T. Kitamori, *Anal. Chem.*, 2002, **74**, 1565.
8 H. Hisamoto, T. Saito, M. Tokeshi, A. Hibara and T. Kitamori, *Chem. Commun.*, 2001, 2662.
9 C. M. Starks, C. L. Liotta and and M. Halpern, in *Phase-Transfer Catalysis*, Chapman & Hall, New York, 1994.
10 E. V. Dehmlow and S. S. Dehmlow, in *Phase Transfer Catalysis*, 3rd Ed. VCH, Weinheim, 1993.
11 K. Manabe, *Tetrahedron*, 1998, **54**, 14465.
12 The same segmented flow was observed in gas–liquid phases in steel microreactor. R. D. Chambers, D. Holling, R. C. H. Spink and G. Sandford, *Lab on a Chip*, 2001, **1**, 132; K. Jähnisch, M. Baerns, V. Hessel, W. Ehrfeld, V. Haverkamp, H. Löwe, C. Wille and A. Guber, *J. Fluorine Chem.*, 2000, **105**, 117.
13 R. Dalpozzo, G. Bartoli, M. Bosco, A. D. Nino, A. Procopio, L. Sambri and A. Tagarelli, *Eur. J. Org. Chem.*, 2001, 2971; J. B. Dorsch and S. M. McElvain, *J. Am. Chem. Soc.*, 1932, **54**, 2960.