The Claisen–Schmidt Reaction Carried Out in Microfluidic Chips

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Received 2 August 2005

Abstract: The Claisen–Schmidt reaction of benzaldehyde in a microfluidic chip has been found to be more efficient than that in a round-bottom flask with vigorous stirring. Slug flow was formed when the organic and aqueous phases were introduced through the microchannel with a width of 300 μm, which provides faster mass transfer than laminar flow.

Key words: microfluidic chips, phase-transfer catalysts, Claisen–Schmidt reaction, benzaldehyde, acetone

Combinatorial chemistry as a high-throughput synthetic technology has became a powerful tool for the discovery of new drugs and materials.[1] Increasing interests have been drawn onto the application of microfluidic chips in this field.[2] Unlike the standard batch systems, the utmost attributes of microfluidic chips include short molecular diffusion distance, large specific interfacial area and small heat capacity, which make chemical reactions carried out in microfluidic chips to be highly effective. In addition, the reagents used and wastes generated in microfluidic chips are much less than that in standard batch systems.

The phase-transfer catalysts (PTCs) have been widely applied in organic synthesis. In the case of phase-transfer reaction, rapid mass transfer of starting material and the produced chemical species across the liquid–liquid interface plays an important role to realize fast chemical reactions with high conversion. Vigorous stirring is the prerequisite for a successful phase-transfer reaction in a round-bottomed flask, which increases the interfacial area and reduces molecular diffusion distance. The microchannel dimensions of microfluidic chips are ideally suited for the phase-transfer reaction. In microchannel, a large interfacial area and short molecular diffusion distance could be obtained without any stirring. It was reported that the phase-transfer diazo-coupling and alkylation reactions in microfluidic chips gave higher yields than that using the standard batch systems even with vigorous stirring.[3] The PTC-catalyzed Claisen–Schmidt reaction of ketones with aldehydes is an important reaction in both academia and industry. In this paper, we report the Claisen–Schmidt reaction of acetone with benzaldehyde performed in microfluidic chips.

The structure of our microfluidic chip is illustrated in Figure 1. The microscale reaction was performed by introducing an ethanol solution containing both acetone (4.0 M) and benzaldehyde (1.0 M), and an aqueous sodium hydroxide solution (0.5 M) through the two inlets of the Y-shaped microfluidic chip with two syringe pumps under continuous flow conditions at ambient temperature. The residence time of the reactants in the microchannel was controlled by varying the total length of the microchannels, while keeping constant the linear flow rate of the organic and aqueous phases. Microfluidic chips with different dimensions were fabricated on soda-lime glass using a photolithographic and wet chemical etching procedure described elsewhere.[4] The channels were etched to a depth of 80 μm with different width of 300 μm and 500 μm, and length of 12, 16, 24, 32, 40, 48, 72, 96 cm. The dependence of the conversion of benzaldehyde to benzylidineacetone on the residence time in microchannels was examined by introducing the reactants into microchannels at the same linear flow rate of 12.0 cm/min and collecting the products from the outlets of the microfluidic chips. The conversions were determined by GCMS. The results, compared with the standard batch system,[5,6] are shown in Figure 2. The conversion increases, as the residence time prolongs. Conversions of 93% and 80% were obtained after an eight-minute reaction in microchannels with the width of 300 μm and 500 μm, respectively. In comparison, 60% conversion was obtained using the standard batch system with vigorous stirring of 1250 rpm. Doubling the reaction time to 16 minutes only increased the conversion to 73%. The outputs obtained from microfluidic chips at the conversion of 93% and from standard batch system at the conversion of 73% were 11 mg/h and 100 mg per run, respectively.

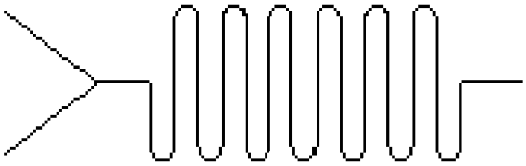

Figure 1 Schematic structure of the microfluidic chip.

The mechanism for Claisen–Schmidt reaction of benzaldehyde with acetone is shown in Figure 3. By carrying out the reaction in microchannels, larger interfacial area and short diffusion distance provide effective molecular diffusion conditions. The distribution of the reactants and the product between the phase–interface in microchannels is faster than in a bulk reaction with vigorous stirring, which allows the product to be transferred into the organic phase from contacting with the base in the aqueous phase.

SYNLETT 2005, No. 20, pp 3163–3165
Advanced online publication: 28.11.2005
DOI: 10.1055/s-2005-922763; Art ID: W00505ST

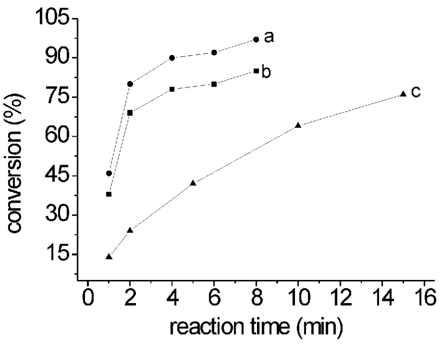

Figure 2 Conversions in microchannels and standard batch system a. 300 μm; b. 500 μm; c. standard batch system.

Therefore, the reaction speed and conversion of Claisen–Schmidt reaction in microfluidic chips were higher than in standard batch systems.

Recently, the formation of plugs in the two-phase flow in microfluidic channels has been studied by the Ismagilov group[7] and also applied in synthesis.[8,3b] Capillary number (Ca) was used to characterize the flow pattern inside the microchannel. Ca is defined as $U\mu/\gamma$, where U [m s^{-1}] is the velocity of the flow, μ [kg m^{-1} s^{-1}] is the viscosity of the flow, γ [kg s^{-2}] is the surface tension at the interface between the aqueous and organic phases. In our experiments, although the capillary numbers in both channels were the same, which is ca. 1.5×10^{-4}, slug flow was formed reproducibly in the 300-μm wide microchannel (Figure 4, a) and laminar flow was formed in the 500-μm wide microchannel (Figure 4, b). The reason remains to be investigated further.

In the laminar flow, two streams flow in the channel side by side. The concentration gradient exists in the radial direction and the mass transfer occurs across an area corresponding to the cross-section of the channel and over a path length equal to half of the channel diameter. In the slug flow, larger interfacial area was formed not only at both ends of the segments but also around the whole droplets, which is generally larger than the channel's cross-sectional area. Therefore, the conversions in the narrower microchannel (Figure 2, curve a) is higher than in the relatively wider microchannel (Figure 2, curve b).

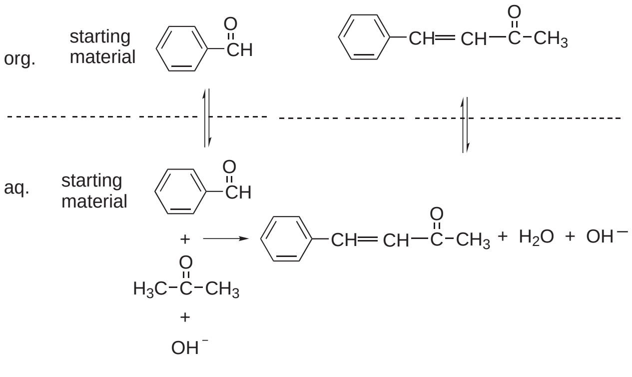

Figure 3 Phase-transfer in the Claisen–Schmidt reaction of benzaldehyde with acetone.

In order to examine the effect of flow rate on the rate of mass transfer between the two phases, the conversions were determined after introducing the reactants at different flow rates through the microchannels with a width of 300 μm. Microfluidic chips with different lengths were used to fix the reaction time at four minutes. In all the flow rates tested, slug flow can be observed. The effect of flow rate on conversion is shown in Figure 5. With the increase of flow rate, the conversion also increased. The higher rate of mass transfer may result from the internal circulation within the slugs, which could be stimulated by the shear between the stationary water at the microchannel wall and the moving organic slugs.

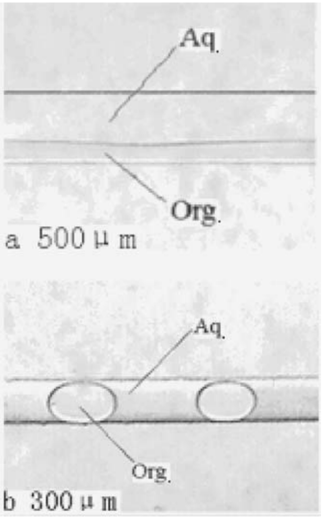

Figure 4 Charge-coupled device (CCD) images of flow type in microchannels with different diameters.

In the standard batch system, N_2 is usually bubbled in order to protect benzyaldehyde from air oxidation. In microfluidic chips, however, the reaction is performed in closed microchannels, the oxidation of benzaldehyde was thus hindered even without N_2.

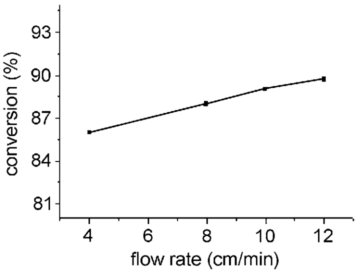

Figure 5 The effect of flow rate on conversion.

In conclusion, herein we report the Claisen–Schmidt reaction carried out in microfluidic chips. Compared with the traditional round-bottom flask, the Claisen–Schmidt reaction of benzaldehyde with acetone in the microfluidic chip was more rapid and efficient due to the fast distribution of the reactants and the product between the phase-interface in microchannels. Furthermore, the smaller (300 μm in width) microchannels gave higher conversions than larger (500 μm in width) microchannels.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (No. 0299030).

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(6) **General Procedure.**
Benzaldehyde (1 mmol), acetone (4 mmol), EtOH (1.0 mL) and aqueous NaOH (0.5 M, 1.0 mL) were placed in a 10-mL round-bottomed flask and stirred at ambient temperature under a N_2 atmosphere. After stirring for period indicated in Figure 2, the reaction was quenched with HCl (0.5 M, 1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with H_2O (5 mL) and dried with Na_2SO_4. The solvent was removed to give benzylidineacetone. The conversion of each period is cited in Figure 2.

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