ABSTRACT
The representative Baylis-Hillman (B-H) reaction of cyclopent-2-enone coupled with 4-nitrobenzaldehyde in the presence of imidazole was accelerated by using electric field as well as temperature manipulation in microreactors. The electric field was used to promote B-H reaction for the first time, the rate was approximately 4.0-fold to 5.2-fold than carried out in conventional vessels.

KEYWORDS: Baylis-Hillman reaction, Microreactor, Rate acceleration, Imidazole

INTRODUCTION
Although the B-H reaction has an extensive application due to the inherent merits, the bottleneck is the slow reaction rate and it will take some days to accomplish (1). For accelerating the reaction rate, many physical and chemical strategies have been employed (2). In recent years, it has been found that organocatalysis as an effective strategy could promote B-H reaction successfully. Especially, the medicine intermediate of imidazole displayed the excellent performance (3).

Meanwhile, miniaturized reactors as a synthetic tools used in bio/chemical reactions have appeared for a long time. Compared to the conventional vessels, the downscaled dimension leads to some important properties which have a fundamental effect on the reactions. With the help of high specific surface areas and small dimension, mass and heat transport are greatly enhanced. Meanwhile, minimal energy and reagent are consumed. In Scheme 1, the considerable rate acceleration of B-H reaction was described involving cyclopent-2-enone and 4-nitrobenzaldehyde catalysed by imidazole in microreactors.

RESULTS AND DISCUSSION
Meanwhile, miniaturized reactors as a synthetic tools used in bio/chemical reactions have appeared for a long time. Compared to the conventional vessels, the downscaled dimension leads to some important properties which have a fundamental effect on the reactions. With the help of high specific surface areas and small dimension, mass and heat transport are greatly enhanced. Meanwhile, minimal energy and reagent are consumed. In Scheme 1, the considerable rate acceleration of B-H reaction was described involving cyclopent-2-enone and 4-nitrobenzaldehyde catalysed by imidazole in microreactors.

The microreactors in this study were home-fabricated by standard photolithography and wet etching with the channel dimension of 150 µm in width, 60 µm in depth and 70 cm in length. The schematic structure of the microreactor is illustrated in Figure 1. The final products containing reactants were diluted by water and determined by capillary micellar electrokinetic chromatography. The comparison of the conversion between microreactors and vials were described in Figure 2. Surprisingly, the conversion increased dramatically with the temperature increasing, which is corresponding to approximately 4.0-fold of rate acceleration compared to the conversion gotten in vials (Figure 3).
Figure 1: The structure of the microreactors
(a: used for temperature and pressure experiment; b: used for electric field experiment).

Figure 2: Comparison of conversions for the reaction carried out in vials and in microreactors.

Figure 3: The effect of temperature on conversion (after reacted in 30 min at each temperature value).

The process of B-H reaction refers to form six-membered transition state via covalent bond (Figure 4). No matter what pathway the reaction experienced, the six-membered or four-membered rings of transition zwitterions always appeared. Thus, we presume that if there is some kind of method that induces the transition zwitterions to generate and convert fastly, the reaction rate will be accelerated. In this study, we readily found that the electric field applied in the reaction solution can realize the hypothesis (Figure 5).
CONCLUSION
Based on microreactors, the rate of B-H reaction was accelerated for 4.0-fold to 5.2-fold than in vials via the flexible manipulation of temperature, pressure and voltage. This reaction presents a sensitive responding to temperature and the conversion reaches the peak value of 59.7% at 90°C. Unlike the temperature, the pressure almost has no obvious effect on this reaction even at the utmost pressure of 5.0 MPa that the microreactor could sustain. However, electric field as a robust and “green” approach was firstly used to accelerate the B-H reaction and display the satisfactory performance, to enlarge this methodology in B-H reaction. It is meaningful to get a thorough understanding of mechanism and screen the scope of substrate in further study.

ACKNOWLEDGEMENTS
The authors gratefully acknowledge the financial support from Ministry of Science and Technology of China (No. 2007CB714504), NSFC (No. 20875091 and No. 20935005) and Chinese Academy of Sciences.

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CONTACT
* Li Qi, Tel: +86-10-82627290, Fax: +86-10-61559373; qili@iccas.ac.cn