www.rsc.org/greenchem | Green Chemistry

Efficient Claisen rearrangement of allyl *para*-substituted phenyl ethers using microreactors†

Lingjie Kong, Qi Lin, Xiaoming Lv, Yongtai Yang, Yu Jia* and Yaming Zhou*
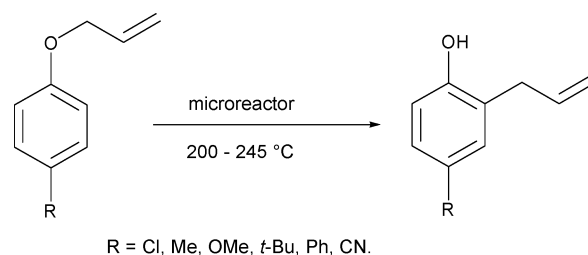
A green way to synthesize allyl phenols has been developed. Quantitative yield of 2-allyl-4-methoxyphenol was obtained *via* a fast Claisen rearrangement in a microreactor system without solvent and work-up.

Organic reactions using microreactors have attracted increasing interest in the past few years.[1–3] The heat transfer efficiency of a conventional reaction system is usually low and causes local overheating, which may lead to formation of impurities. Microreactor systems, in contrast, have excellent heat transfer characteristic. The surface area-to-volume ratio of a microreactor is up to $10\,000$–$50\,000$ m^2 m^{-3}, which is larger than a conventional reaction vessel by up to two magnitudes.[4,5] Therefore, the heat exchange between the reaction mixtures passing through the micro-channels and the external environment is very efficient, and the heat transfer value reaches the order of 10 kWm^{-2} K^{-1}.[5] The temperature of the reaction mixture in a microreactor system is able to achieve an even distribution that local overheating can be easily avoided.[6] As a result, compared to the traditional reaction systems, products with less impurities, higher yields and/or higher selectivity can be generated in microreactor systems.[7–9] A microreactor system is also a naturally closed system. The material exchange of the reaction mixture with the external environment is avoided without any additional protection (*i.e.* inert gas protection).

In recent years, a number of studies on organic reactions using microreactor systems have been done.[10–12] It has covered various reaction types, including nitration,[13] Wittig reaction,[14] Newman-Kwart rearrangement,[15] fluorination[16] and coupling reactions,[17,18] *etc.* However, the study of Claisen rearrangement reactions in microreactors at high temperatures has been few reported so far.[19]

The Claisen rearrangement (Scheme 1) is a powerful reaction for carbon–carbon bond formation. The Claisen rearrangement of allyl *para*-substituted phenyl ethers usually requires high temperatures (*e.g.* 200 °C) and long reaction times under conventional conditions.[20] Long exposure times of the reaction mixtures to uneven heating at high temperatures is problematic, and may cause the formation of many impurities. In addition, at such a high temperature severe carbonization becomes a problem that results in undesired products and therefore low yields and tedious work-ups. Some successful applications of Lewis Acid catalyzed Claisen rearrangements to reduce reaction

Department of Chemistry, Fudan University, Shanghai, 200433, P. R. China. E-mail: yujia@fudan.edu.cn
† Electronic supplementary information (ESI) available: Experimental data. See DOI: 10.1039/b822513c

Scheme 1 The Claisen rearrangement of allyl *para*-substituted phenyl ethers in a microreactor system.

temperatures significantly have been reported.[21,22] However, the catalyst used, such as SnCl$_2$ and BCl$_3$, are toxic and moisture sensitive. To shorten the reaction time while maintaining high reaction temperatures is another way to solve the above mentioned problems that exists in the Claisen rearrangement. Besides the use of ionic liquid as solvent reported recently,[23] we postulated that this approach can also be achieved in a greener way by using a microreactor. Here we report efficient Claisen rearrangement of allyl *para*-substituted phenyl ethers in microreactor systems, by which several allyl phenols have been prepared with high purities without any solvent and work-up.

The microchannel we used is one kind of stainless steel pipe that is commonly used in high-performance liquid chromatography (HPLC). It is acid/base resistant and high-temperature endurable. We fabricated a microreactor system, MR-1, with a pump connected micro syringe (0.005-36 ml h^{-1}) and a 120 cm long pipe (170 μm in id) with a maximal heating length of 106 cm. The necessary cooling and collection devices linked in sequence following the reaction section. The substrate is injected through the pipe, heated in the oil bath, subsequently cooled in the second bath, and finally collected from the other end of the pipe.

We used *p*-chlorophenyl allyl ether (substrate **1**) as our model substrate for the optimization of Claisen rearrangement in the microreactor MR-**1** (Fig. 1). The effect of temperature and residence time on the reaction yield was studied. We started with a moderate temperature, 200 °C, for the rearrangement, considering the great heat transfer efficiency of the microreactor. We explored the effect of different residence time, from 8 min to 24 min with 4 min interval, on the reaction by adjusting the flow rate of the substrate at this temperature.
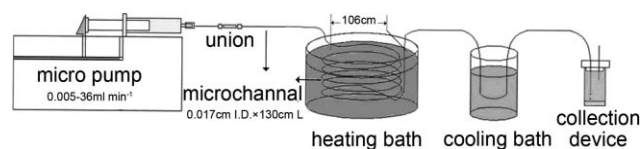

Fig. 1 The microreaction system 1 (**MR-1**).

We found that at 200 °C, the yield of 2-allyl-4-chlorophenol increased along with the residence time to reach 35% for 24 min. Longer residence time led to a slow increase in yield (*e.g.* 37% for 30 min) (Fig. 2).
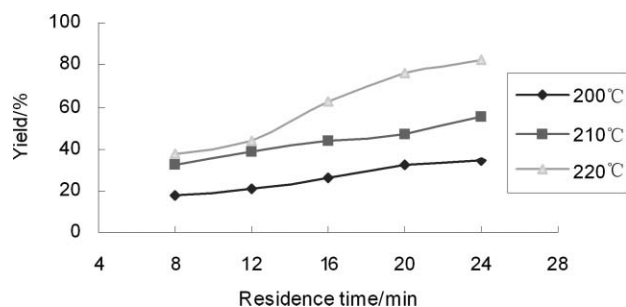

Fig. 2 Effect of residence time on the yield of the reactions of substrate **1** at different temperatures.

When the temperature was raised to 210 °C, the yields with different residence time increased correspondingly. This might indicate that even in the microreactor system, the temperature is still a key factor for an efficient rearrangement reaction. Therefore, we further enhanced the reaction temperature. At 220 °C, even higher yields were obtained. When the residence

time was 24 min, compound **1** was generated in 82% yield, unlike the conventional Claisen rearrangement reaction, which gave only 14% yield (entry 1, Table 1). Both ^{1}H NMR and HPLC showed that there are only two components in the crude product of microreaction: the unreacted starting material and the target product.

We believe this high reaction efficiency primarily benefits from the excellent heat exchange in the microreactor: the substrate reaches the energy threshold of the reaction immediately after it flows into the heated part of the microchannel. In addition, unlike the conventional reaction, the reaction in a microreactor is a continuous process in the channel, in which the product flows out of the reaction system immediately after the reaction has occurred. Therefore, the reaction time is shortened, so is the contract time of the reaction mixture with the heat source. The chance of overheating and decomposition/carbonization of the substrate and product may be reduced. Moreover, the closed system design of the microreactor system that isolates the reaction system from the external air may prevent possible oxidation. Longer residences times were also tested. For example, a reaction for 36 min was tried. However, there was not much improvement in yield. This indicates that the reaction completed within 24 min at this temperature, and further extension of the residence time does not necessarily increase the yield.

Table 1 Claisen rearrangement of allyl *para*-substituted phenyl ethers by using microreactors and conventional reactors

Entry	Substrate	Product	Residence time/min	T/°C	Yield^a (%) Microreaction	Conventional reaction^d	
1	Cl	Cl	24	220	82	14	78 (3 h)
			36	220	83		
2	Me	Me	24	200	69	2	34 (3 h)
			36	200	73		
3	*t*-Bu	*t*-Bu	24	225	94		
			36	225	97	39	83 (3 h)
4	OMe	OMe	20	220	Quant.^{b}		
			24	220	Quant.^{b}	32	80 (3 h)
5	Ph	Ph	24	230	77^c		
			24	240	90^c	37^c	71 (3 h)
6	CN	CN	24	235	80^c		
			24	245	93^c	43^c	69 (3 h)

^{a} Determined by HPLC. ^{b} No purification required. ^{c} Use diphenylether as solvent. ^{d} For each substrate (5 mmol) or the solution of the solid substrate (5 mmol), the conventional reaction was performed in a reflux device at the same temperature for the same reaction time (corresponding residence time of the microreaction) as in the microreactor, and both the temperature and reaction time are the optimized ones for the microreaction.

To this point, we have developed a solvent-free method to efficiently synthesize 2-allyl-4-chlorophenol *via* Claisen rearrangement in a microreactor system in high yield within a short reaction time. The optimal conditions we have found include a short but sufficient residence time and a temperature near the boiling point of the substrate. Based upon these findings, we continued our study on a number of other *para*-substituted substrates (Table 1) using our optimized conditions. Since there are some differences in the chemical properties among the substrates, residence times of both 24 min and 36 min were tested for these reactions.

The results are summarized in Table 1. The reaction of substrate **2** gave a relatively moderate yield (entry 2). It is due to the low reaction temperature, which is limited by the low boiling point of the substrate (~210 °C). However, it is still greatly superior to the corresponding reaction in a conventional reactor. The reactions of substrates **3** and **4** gave excellent results (entries 3 and 4). The purities of these two products were so high that neither work-up nor purification was needed. Further studies on substrate **4**, 2-allyl-4-methoxyl-phenol, showed that less residence time (*i.e.* 20 min) also gave a nearly quantitative yield, and an even shorter residence time (12 min) still led to an excellent yield (98%, Fig. 3).

The above reaction substrates are all liquid at room temperature, and undergo solvent-free reaction very well in the microreactor system. In order to expand the application of this new reaction platform, we also used two solid substrates, **5** and **6**. A high boiling point ether Ph₂O was used as solvent. In order to obtain the maximum efficiency of our microreactor, we used the least amount of solvent for preparing the most concentrated solution of the substrate in Ph₂O. These approaches gave yields of 90% and 93%, respectively (entries 5 and 6).
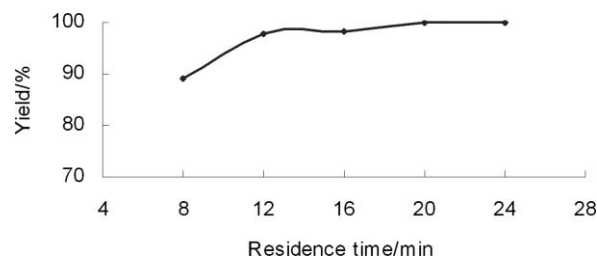

Fig. 3 Effect of residence time on the yield of the reaction of substrate **4** at 220 °C.

In order to compare with the microreactions, the conventional reactions of substrates **1–6** in a hot reflux system were also tested for both the same time (residence time) and typical long time (3 h). The yields of conventional reactions for the same time as microreaction were no more than 43%, which is only 1/3 to 1/2 of those in a microreactor system. Even when the reaction time was increased to 3 h, the yields were much lower than those of microreactions. In addition, the microreaction crude product is pellucid, while the conventional crude product is black and viscous. Several impurities formed in the conventional reaction are observable in the HPLC traces (Fig. 4) (see Fig. 5 for an example of substrate **6**).

The influence of the substrate flow rate in the microchannel was also explored in addition to the reaction temperature and residence time. For each microreactor with a fixed heating length, the residence time and flow rate of the substrate can not be changed at the same time (heating length ∝ residence time × flow rate). Therefore, we set up microreactor MR-**2**, which was fabricated by the same way as MR-**1** except that its heating length is twice as that of MR-**1**. When the residence time is the same, the flowing velocity of the substrate in MR-**2** is twice as
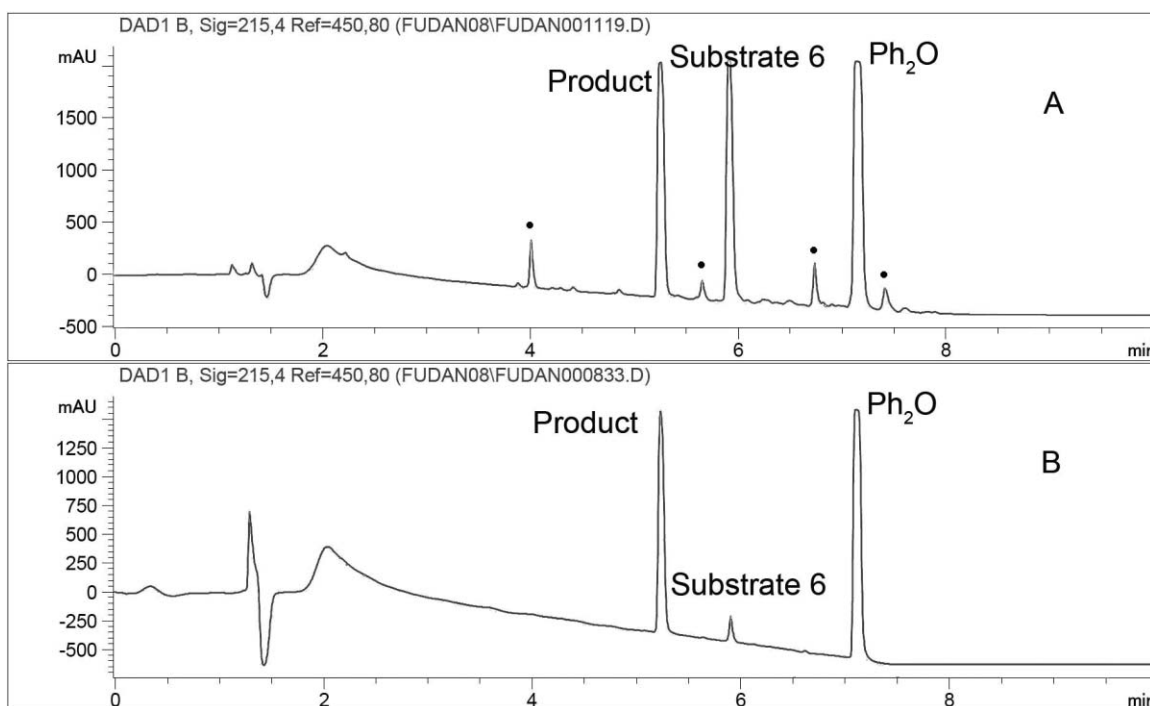

Fig. 4 Comparative HPLC traces of Claisen rearrangement reaction mixtures of substrate **6** (use Ph₂O as solvent) in a conventional hot reflux device (A) or a microreactor (B). ● indicates unidentified impurities. Reading at 215 nm.
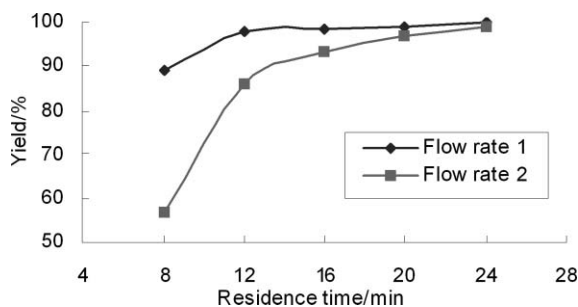
Fig. 5 Effect of flow rate on the yield of reaction of substrate **4** at 220 °C (flow rate 1 = 0.06 ml min^{-1}; flow rate 2 = 0.12 ml min^{-1}).

fast as that in MR-**1**. We used substrate **4** as a model substrate, and performed parallel reactions at 220 °C with the residence time from 8 to 24 min with 4 min interval.

We found that the yield is affected by the substrate flow rate (Fig. 5). In general, lower flow rates gave better yields with the fixed residence time. However, the difference in yield between the two microreactors decreased while the residence time increased. With a residence time of 8 min, the difference was more than 30%; when the residence time is more than 24 min, the yields at the two flow rates are approximately the same. The result is proven by the similar data obtained from a careful repetition of the experiments.

In conclusion, Claisen rearrangement has been studied in microreactors. We have developed a new green synthetic platform in a microreactor system to synthesize allyl *para*-substituted phenyl phenols *via* Claisen rearrangement in high efficiency. Compared with the conventional method, much higher yields and purities have been obtained within much shorter reaction time. Studies on more substrates of different classes are on the way to expand the application of this platform. In addition, we have demonstrated the impact of flow rate on the reaction. More studies on the flow rate are undergoing for a better understanding of the mechanism.

Acknowledgements

Notes and references

1 B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan and D. T. McQuade, *Chem. Rev.*, 2007, **107**, 2300–2318.
2 B. Ahmed-Omer, J. C. Brandt and T. Wirth, *Org. Biomol. Chem.*, 2007, **5**, 733–740.
3 P. Watts and S. J. Haswell, *Chem. Soc. Rev.*, 2005, **34**, 235–246.
4 K. P. JNckel, Microsystem Technology for Chemical and Biological Microreactors, in *DECHEMA Monographs*, Ed. W. Ehrfeld, VCH, Weinheim, 1996, p. 29.
5 K. Jahnisch, V. Hessel, H. Lowe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406–446.
6 S. C. Wang, C. Y. Lee and H. P. Chen, *J. Chromatogr., A*, 2006, **1111**, 252–257.
7 K. Wang, Y. C. Lu, H. W. Shao and G. S. Luo, *Ind. Eng. Chem. Res.*, 2008, **47**, 4683–4688.
8 A. Hartung, M. A. Keane and A. Kraft, *J. Org. Chem.*, 2007, **72**, 10235–10238.
9 H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami and J. Yoshida, *J. Am. Chem. Soc.*, 2007, **129**, 3046–3047.
10 P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong and X. L. Zhang, *Tetrahedron*, 2002, **58**, 4735–4757.
11 K. Geyer, J. D. C. Codee and P. H. Seeberger, *Chem.–Eur. J.*, 2006, **12**, 8434–8442.
12 See an online database of flow chamistry at http://www.flowreact.com.
13 L. Ducry and D. M. Roberge, *Angew. Chem., Int. Ed.*, 2005, **44**, 7972–7975.
14 V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington and S. Y. F. Wong, *Analyst*, 2001, **126**, 7–10.
15 U. Tilstam, T. Defrance and T. Giard, *Org. Process Res. Dev.*, 2009, **13**, 321–323.
16 T. Gustafsson, R. Gilmour and P. H. Seeberger, *Chem. Commun.*, 2008, 3022–3024.
17 C. Basheer, F. Shahitha, J. Hussain, H. K. Lee and S. Valiyaveettil, *Tetrahedron Lett.*, 2004, **45**, 7297–7300.
18 B. K. Singh, N. Kaval, S. Tomar, E. Van der Eycken and V. S. Parmar, *Org. Process Res. Dev.*, 2008, **12**, 468–474.
19 S. Ceylan, C. Friese, C. Lammel, K. Mazac and A. Kirschning, *Angew. Chem., Int. Ed.*, 2008, **47**, 8950–8953.
20 A. M. Martin Castro, *Chem. Rev.*, 2004, **104**, 2939–3002.
21 K. M. Anderson, L. Jaquinod, M. A. Jensen, N. Ngo and R. W. Davis, *J. Org. Chem.*, 2007, **72**, 9875–9880.
22 D. Sarkar and R. V. Venkateswaran, *Synlett*, 2008, 653–654.
23 X. X. Han and D. W. Armstrong, *Org. Lett.*, 2005, **7**, 4205–4208.