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Continuous synthesis of Gabapentin with a microreaction system

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HIGHLIGHTS

- Hofmann rearrangement was achieved continuously by one-step microreaction process.
- An apparent kinetic model was proposed to optimize the operation conditions.
- The concentration of NaOH has a smaller effect than NaClO on the reaction rate.

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ABSTRACT

In this paper, a microreaction system was developed to intensify the synthesis process of Gabapentin. Due to the high mass and heat transfer performance, Hofmann rearrangement can be achieved continuously by one-step microreaction process at relatively high temperature (40–45 °C) with a residence time (5–7 min) much shorter than the conventional 4–5 h in batch reactors. By studying the effects of concentration and temperature on the reaction rate, an apparent kinetic model was developed to help understanding the whole process deeply and optimizing the operation conditions.

1. Introduction

Hofmann rearrangement is an organic reaction that converts a primary amide to a primary amine with one fewer carbon atom (Hofmann, 1881; Shioiri, 1991). This reaction has been reported to be a key step in the alternative total synthesis of many pharmaceutical active ingredients like Oseltamivir (Satoh et al., 2007), Epibatidine (Evans et al., 2001) and Gabapentin (Kumar et al., 2008).

Gabapentin is mainly used to treat epilepsy and neuropathic pain (Backonja et al., 1998; Dworkin et al., 2007). Currently, the annual output of Gabapentin produced is very considerable, in excess of 1000 tons. Therefore, there is a strong demand to develop a more efficient and economical production technique. Hofmann rearrangement plays an important role in the synthesis of Gabapentin that converts 1,1-cyclohexanediacetic acid monoamide (CAM) to 1-(aminomethyl)cyclohexaneacetic acid (Gabapentin), as shown in Fig. 1.

In the existing synthetic process, this reaction is performed with classic methods involving batch technology (Bercovici et al., 2003; Cannata et al., 2002). Since the reaction of Hofmann rearrangement in this case is strongly exothermic, in batch reactors, the reagents have to come into contact carefully at low temperature (−5–5 °C) to prevent local reacting acceleration and local overheating. Then, a higher temperature condition is needed for hydrolysis of the intermediate product (isocyanate) to obtain the product. The whole procedure is similar to the procedure in laboratory synthesis, which may not be commercial achievable and efficient in practice. The low reaction temperature at the early stage requires lots of energy for cooling down and also leads to a low reaction rate, which causes a long reaction period of 4–5 h. Moreover, much more oxidants and bases are used to accelerate reaction rates at low temperature, imposing a burden on wastewater treatment.

According to the mechanism of Hofmann rearrangement (Wallis and Lane, 1946) (Fig. 2), it can be seen that oxidants and bases act on the first and second steps of the reaction respectively. So it is very important to achieve homogeneous distributions of bases and oxidants at the beginning of reaction in order to increase reaction rate and inhibit local overheating, which means a quick and well mixing is needed. Meanwhile, reaction temperature is also a key factor in this process. In view of the slow decomposition of sodium hypochlorite under alkaline conditions even in 50 °C (Lister, 1956), an appropriate rise in temperature helps accelerate the reaction, while reaction temperature too high may lead to

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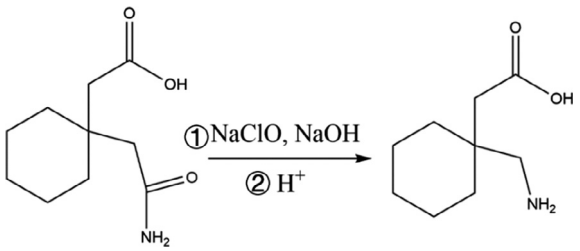

Fig. 1. The Hofmann rearrangement in the synthesis of Gabapentin.

the formation of by-products. Therefore, precise temperature control is needed to intensify this process.

Considering the limitation of a batch reactor on mixing and temperature control, the development of microreaction technology provides a new and efficient approach to achieve the Hofmann rearrangement. Over the last two decades, microreaction technology has been applied to different basic researches and industrial applications (Jensen, 2017; Kashid and Kiwi-Minsker, 2009). And many reaction processes have been enhanced, such as Beckmann rearrangement (Zhang et al., 2014), Claisen rearrangement (Sato et al., 2009) and Sonogashira coupling (Kawanami et al., 2007). Compared to batch reactors, microreactors have superior advantages such as enhanced mixing performance, accurate control of reaction temperature and time, and safety (Kiwi-Minsker and Renken, 2005; Mark et al., 2010). Moreover, as a continuous process, microreaction technology has the great potential in automatic control and easy scale-up (Jensen, 2017; Kockmann et al., 2011; Kockmann and Roberge, 2011).

In a commercially available microfluidic flow chemistry platform, Ley et al. confirmed the feasibility of converting the amide into the corresponding carbamates at 120 °C with considerable yields via a reaction similar to Hofmann rearrangement (Palmieri et al., 2009). However, the reactions were carried out on a 50–100 μg scale with dilute concentrations, which was hard to satisfy the demand of product synthesis. Herein, we developed a more practical and easy scale-up micro-reactor device that can run on a relatively large flow range with high concentrations.

On the other hand, microreaction technology is also an attractive tool for kinetics measurements (Hessel et al., 2011; Khan et al., 2015; Salmi et al., 2013). Due to the superior advantages mentioned above, more precise kinetic data can be obtained easily by a microreactor (Dong et al., 2015; Wang et al., 2015), particularly for fast reactions (Han et al., 2009; Wang et al., 2011). With the well understanding of reaction kinetics of Hofmann rearrangement, it will be easier to further realize and optimize this reaction process in industry. However, to the best of our knowledge, the kinetic model of Hofmann rearrangement has not been reported, even an empirical kinetic model. Therefore, it is very necessary to study the kinetics of Hofmann rearrangement.

In this paper, we focused on the process intensification of Gabapentin synthesis using a microreaction system. Meanwhile, we systematically studied the effects of concentration and reaction temperature on the reaction rate. Finally, an apparent kinetic model was developed to help understanding the reaction process deeply and optimizing the operation conditions.

2. Material and method

2.1. Preparation of reactant solutions

Sodium hydroxide (AR) was purchased from Xilong Scientific Co., Ltd. Sodium hypochlorite (6–14% active chlorine basis) and sodium thiosulfate pentahydrate (ACS) were purchased from

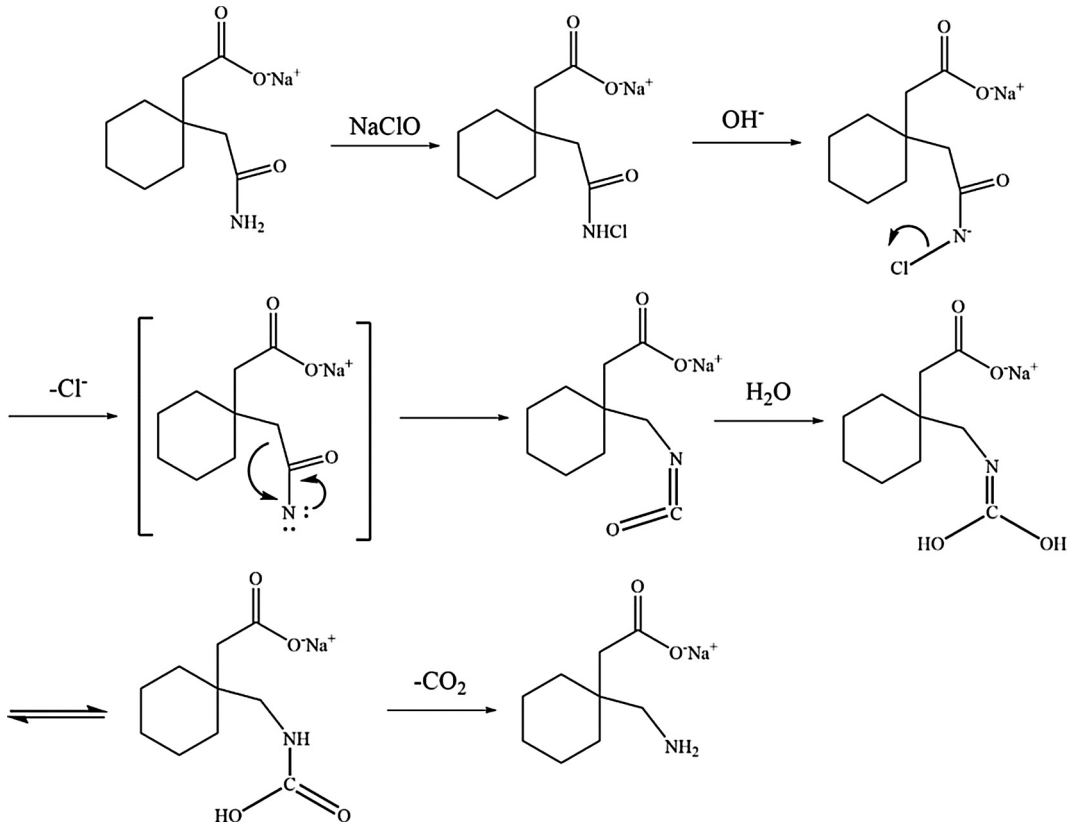

Fig. 2. Mechanism of Hofmann rearrangement.