Gram-to-Kilogram Scale-Up Synthesis of 2,2'-Diallylbisphenol through a Microchannel Reactor

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ABSTRACT*: A continuous-flow synthetic platform utilizing a microchannel reactor was developed here to realize the gram-to-kilogram scale-up synthesis of 2,2'-diallylbisphenol A (DABPA) via thermal Claisen rearrangement with high efficiency and safety. The optimal reaction temperature of this thermal rearrangement was confirmed firstly by differential scanning calorimetry and then the classical batch synthesis was carried out to find that large quantities of reaction heat were accumulated, which not only promoted the formation of many by-products but also would bring various uncontrollable risks such as bumping. Thus a simple continuous flow synthetic platform was constructed which employed a microchannel as the reactor. The optimal working temperature of this reactor and the flow velocity of the reactant were screened and established. Compared with the conventional batch method, the utilizing of a flow reactor avoided a large amount of reactant staying in the reaction mixture and minimized the accumulation of reaction heat, which not only enhanced the safety of the reaction process but also prevented the formation of many by-products, delivering a practical strategy for the scale-up synthesis of DABPA.*

KEYWORDS*: 2,2'-Diallylbisphenol A; Claisen rearrangement; Continuous flow; Microchannel; Scale up synthesis.*

INTRODUCTION

2,2'-Diallylbisphenol A (DABPA), an important reactive functional molecule that has been widely used in epoxy resin and bismaleimide (DMI) [1,2] as it can toughen these resins thus to promote the application of these materials in aerospace and electronics industries. Besides, this building block can also be used to construct functional materials for high-performance alkaline fuel cells [3], vapour sensors [4], proton exchange membranes [5], and so on. Thus a practical method was developed to synthesize this compound which contained two steps: (i) Synthesis of bisphenol A bisallyl ether through Williamson ether synthesis method by utilizing bisphenol A and allyl chloride/bromide as starting materials. (ii) Thermal Claisen rearrangement of compound bisphenol A bisallyl to afford the target molecule DABPA [6]. Many previous reports indicated that the yield of the first step

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1021-9986/2023/10/3227-3233 7/$/5.07

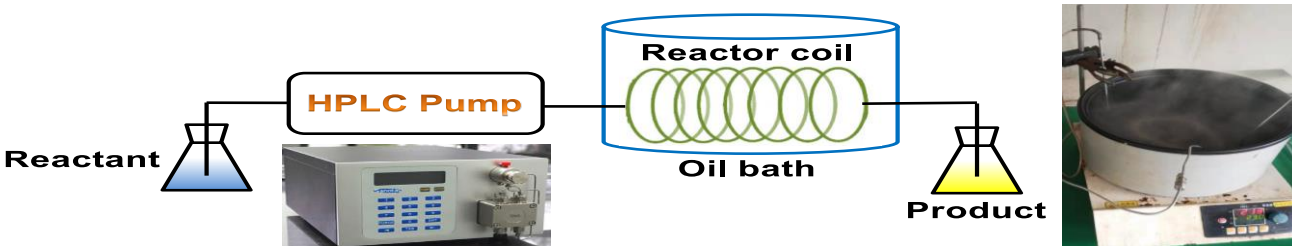
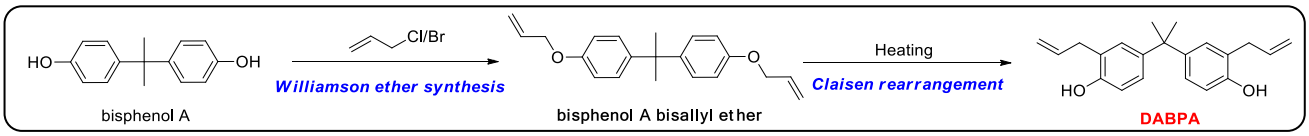


Fig. 1: Simple mic rochannel flow reactor system



Scheme 1: Synthetic route to DABPA

was very high and the reaction was easy to handle. It seems like the Claisen rearrangement reaction was the key step of the synthetic route. Therefore, we mainly focused on the second step, and a 100-gram scale-up preparation of the target molecule was carried out by utilizing a round bottom flask as a reactor. It is noted that this reaction was an exothermic reaction that took place at a high temperature and huge heat was emitted when the reaction began which increased the reaction temperature rapidly, not only promoting the formation of many by-products but also making the scale-up of this reaction to kilogram very dangerous as the overheated system will bring various uncontrollable risks. Hence, developing a new synthetic process of this thermal rearrangement that can eliminate the security risk is extremely urgent. The aim of this research was to solve the problem that scale-up synthesis of DABPA through batch chemistry suffers from the strongly exothermic effect which not only prevents access to qualified products but also brings various uncontrollable risks.

Over the past decade, flow chemistry developed fast as it can make the reaction process safer and faster with high selectivity and high reproducibility than the traditional batch manner [7–11]. This synthetic tool has been used in the synthesis of many chemicals such as heterocycles [12], natural products [13], and pharmaceuticals [14,15], and the outcomes of various reactions can be improved by utilizing this technique such as purification[16], C–H functionalization [17,18], photo rearrangements [19] and halogenations [20,21]. What's more, some Claisen rearrangement reactions have been achieved by microreactor [22–26] which have aroused our great concern as this chemical technology could tolerate several harsh reaction conditions such as high temperature/pressure. Thus, we turned to seek a commercially available microreactor to carry out the scale-up synthesis of DABPA.

However, many commercial microreactors based on glass or silicon carbide cannot run at temperatures above 200 °C due to limitations in heat transfer systems [25]. Thus, a simple microchannel flow reactor system (Fig. 1) was constructed in this article to solve the strongly exothermic effect of this Claisen rearrangement reaction and the gram-to-kilogram scale-up synthesis of DABPA has been accomplished. Both the temperature of the oil bath (reaction temperature) and the residence time of the reactant stay in the reactor (reactant flow velocity) were optimized in this paper to improve the conversion rate of the reaction. Compared with the traditional batch reaction, only a small amount of reactant was allowed to flow quickly through the stainless-steel coil reactor of this synthetic system thus minimizing the accumulation of large quantities of reaction heat, which not only enhance the safety of the reaction process but also depressed the formation of some by-products, providing an alternative synthesis technology of DABPA.

EXPERIMENTAL SECTION

Materials, characterization and instruments

Bisphenol A, potassium carbonate (K_2CO_3), allyl chloride, ethanol, toluene, and *n*-heptane were purchased from Sinopharm Chemical Reagent Co. (Shanghai, China) and used as received. ^1H and ^{13}C NMR spectra were measured using a Bruker AV500 MHz (Bruker Biospin GmbH, Rheinstetten, Germany) spectrometer (internal reference: $CDCl_3$). The mass spectra (MS) were recorded on a gas chromatograph-mass spectrometer (Agilent 7000C, GC–MS/MS, Agilent Technologies, Santa Clara, CA, USA) with *m*/*z* 50–650. A 250 mL three-necked round

Table 1: Optimization of reaction conditions by DSC

Entry	Reaction conditions	Yield (HPLC, % area)
1	210 °C (10 mins)	2.3%
2	220 °C (10 mins)	6.2%
3	230 °C (10 mins)	24.1%
4	240 °C (10 mins)	62.7%
5	250 °C (10 mins)	79.3%
6	260 °C (10 mins)	76.1%
7	250 °C (5 mins)	59.4%
8	260 °C (5 mins)	74.1%
9	230 °C (60 mins)	77.5%
10	240 °C (60 mins)	76.8%
11	250 °C (8 mins)	75.5%
12	250 °C (12 mins)	78.9%
13	250 °C (15 mins)	78.9%
14	250 °C (20 mins)	77.8%
15	250 °C (25 mins)	74.3%
16	250 °C (30 mins)	74.0%

bottom flask was used as a reactor when we carried out experiments through batch chemistry. The reactant used in the flow reaction was transported by a plunger pump (AP0010, Sanotac, Shanghai, China). The coil used as a microchannel reactor was made up of stainless steel and its length was 10 meters and its inner diameter was 1.5 millimeters.

Synthesis

As shown in Scheme 1, DABPA was synthesized through two steps: the first one was a Williamson ether synthesis reaction and the second one was a thermal Claisen rearrangement reaction.

Synthesis of bisphenol a bisallyl ether through batch chemistry

Bisphenol A (11.42 g, 50 mmol, 1.0 eq.), potassium carbonate (20.73 g, 150 mmol, 3.0 eq.), allyl chloride (8.03 g, 105 mmol, 2.1 eq.) and ethanol (100 mL) were added to a three-necked round bottom flask under N_2. Then the reaction mixture was heated to reflux under nitrogen for 8 hours before cooling to room temperature. The salt of the reaction was then removed by filtration to afford the filtrate. The solvent was then removed under vacuum and the obtained residue was further purified by column chromatography on silica gel (ratio: petroleum ether/ethyl acetate = 20/1, V/V) to provide the product bisphenol A bisallyl ether as colorless liquid (14.65 g，95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.14–7.13 (m, 4H), 6.83–6.81 (m, 4H), 6.09–6.02 (m, 2H), 5.43–5.39 (m, 2H), 5.28 (dd, J = 10.5 Hz, J = 1.5 Hz, 2H), 4.52–4.51 (m, 4H), 1.64 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 143.4, 133.7, 127.9, 117.7, 114.2, 69.0, 41.8, 31.2 ppm. MS m/z (RI, %): 308.1 (M^+, 25.5), 293.1 (100), 294.1 (21.2), 211.0 (10.6), 252.0 (6.8), 309.1 (5.6).

Ten-gram-scale synthesis of DABPA through batch chemistry

To a round bottom flask was added bisphenol A bisallyl ether (10.00 g, 32.4 mmol) under nitrogen. Then the reaction mixture was started to be heated on an electric heating sleeve which was set at 250 °C. The reaction was monitored after a time interval by HPLC to analyze the conversion of the substrate. At last, a sample from the reaction mixture was taken and used to identify the structure of the final product which was further purified by column chromatography on silica gel (ratio: petroleum ether/ethyl acetate = 4/1, V/V) to provide the product DABPA as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98–6.96 (m, 4H), 6.71 (d, J = 8.5 Hz, 2H), 6.04–5.96 (m, 2H), 5.15–5.14 (m, 2H), 5.12 (t, J = 1.5 Hz, 2H), 4.94–4.93 (m, 2H), 3.37 (d, J = 6.5 Hz, 2H), 1.62 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1, 143.6, 136.8, 128.9, 126.4, 124.5, 116.4, 115.4, 41.9, 35.6, 31.3 ppm. MS m/z (RI, %): 308.1 (M^+, 21.0), 293.1 (100), 294.1 (22.1), 159.0 (11.8), 44.1 (10.9), 91.0 (6.0).

RESULTS AND DISCUSSION

As shown in Scheme 1, DABPA was synthesized through two steps and the first one was a Williamson ether synthesis reaction which was verified by employing bisphenol A and allyl chloride as the reactant, potassium carbonate as base, and ethanol as solvent. We found that the yield of this reaction was very high, which was by previous reports [6]. Therefore we mainly focused on the second step and started to investigate the reaction temperature and reaction time as these two factors were the key points of thermal Claisen rearrangement.

Exploring the optimal reaction temperature by DSC

The optimal reaction temperature and reaction time were screened by carrying out microscale thermal rearrangement reactions on DSC (differential scanning calorimeter) and the obtained results were presented in Table 1. Consistent with the previous reports, this thermal

Table 2: Conversion of ten gram-scale synthesis in a batch reactor under different reaction times

Entry	Reaction time	Yield (HPLC, % area)
1	1 h	70.4%
2	3 h	63.6%
3	5 h	49.4%

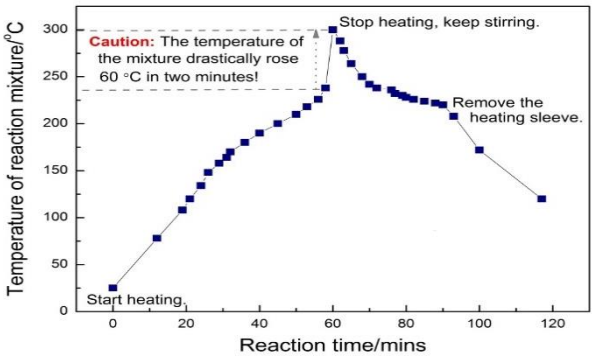


Fig. 2: Reaction temperature versus reaction time curve of 100 gram scale-up preparation of DABPA

rearrangement began at a relatively high temperature (>200 °C) and when the reaction temperature rose the HPLC yield of the reaction improved (entries 1-4). The optimal reaction temperature was 250 °C (entry 5) and further raising the reaction temperature would slightly decrease the HPLC yield (entry 6). Then the suitable reaction time was examined (entries 8-16) and found that if the reaction was set at 10 to 15 minutes, similar high yields (78.9%~79.3%) were received. If the reaction time was prolonged, lower yields were obtained (entries 14-16) which were caused by the formation of some by-products.

Batch chemistry

With the optimized batch reaction conditions now in hand, we carried out a ten-gram-scale synthesis reaction through a traditional batch reactor (round bottom flask). The temperature of the electric heating sleeve used in this reaction was set at 250 °C and this gram-scale reaction went well. The results were summarized in Table 2 which were in accordance with the results given by DSC that prolonging the reaction time will promote the formation of some by-products thus depressing the yields.

Then we used the same reaction conditions to try 100 g scale-up preparation of DABPA. The obtained curve of reaction mixture temperature versus time is illustrated in Fig. 2. As we can see a relatively flat curve was observed until the temperature of the reaction system reached 210 °C. When the reaction began, the temperature of the reaction mixture drastically raised 60 °C within two minutes. The color of the reaction turned to get black and this phenomenon was not observed when we carried out the 10-gram scale-up reaction. Therefore, we stopped heating the reaction mixture and left it to cool down slowly. Despite this reaction could be accelerated by its exotherm, the rapid growth of the internal temperature would promote the formation of many by-products. Moreover, the overheated system will bring various uncontrollable risks such as bumping, which may harm the experimenter. These results indicated that we cannot scale-up of this reaction to kilogram simply through a batch process and a safer strategy must be adopted.

Continuous flow chemistry

We carefully analyzed the results of the batch scale-up synthesis and found the key point of this reaction was how to improve the heat transfer efficiency. Thus, we turned to solve this problem by utilizing a micro-reactor system as specific surface areas of micro-structure far outweigh the traditional reactor's, which might avoid local overheating [27, 28]. What's more, both the reactant and product are liquids and this reaction needs no solvent and catalyst, which were beneficial to the material transfer in the microchannel by the pump. Firstly, we tried to seek a commercial microreactor but found most of them (based on glass or silicon carbide) cannot tolerate high temperatures above 200 °C [25]. Thus, we constructed a simple microchannel flow reactor system that consisted of five units.

The HPLC pump was used to transport the reactant bisphenol A bisallyl ether. The microchannel coil we used was made up of stainless-steel pipe which was high-temperature endurable. Both the length of the coil and the flow velocity of the reactant could be adjusted thus to control the residence time. Moreover, this closed stainless steel coil could isolate the reaction mixture from the external air, which could prevent the possible oxidation of the olefin as a batch process of this reaction often needs inert gas protection. The oil bath was used to heat the stainless-steel pipe reactor whose temperature could be adjusted and regarded as the temperature of the reaction. At last, the final product, DABPA could be collected from the end of the pipe.

Table 3: Effect of substrate flow velocity on the yields of the scale-up reaction

Entry	Temperature (oil bath/)	Flow velocity (mL/min)	Yield (HPLC, % area)
1	250 ºC	2.0	61.4
2	250 ºC	3.0	65.9
3	250 ºC	4.0	68.7
4	250 ºC	5.0	69.6
5	250 ºC	6.0	72.5
6	250 ºC	7.0	68.6
7	250 ºC	5.8	69.5
8	230 ºC	5.8	14.4

We set the temperature of the oil bath at 250 ºC as we used DSC to ensure that the optimal reaction temperature of this rearrangement was 250 ºC and then the effect of the flow velocity (residence time) of the substrate on the reaction yields was studied. The results are shown in Table 3. As we can see when the flow velocity of the bisphenol A bisallyl ether increased to 6.0 mL/min, the highest yield 72.5% was obtained (entries 1-5). Further increased flow velocity would result in result some unreacted material which lowered the conversion (entry 6). If the flow velocity was slightly lowered, a decrease in the yield was observed (entry 7). In contrast, a relatively low yield was obtained when the system was cooled to 230 ºC (entry 8).

After the reaction was smoothly running under the optimized flow reaction conditions for a while, a clean receiving flask was put at the end of the coil and initiated a kilogram scale-up synthesis of DABPA. The oil temperature was detected on time and the temperatures remained stable during this scale-up. Three hours later, more than 1 L DABPA was obtained. It seems that compared with the conventional batch style, the utilizing of the flow reactor avoided a large amount of reactant staying in the reaction mixture and minimized the accumulation of large quantities of reaction heat, enhancing the safety of the reaction process.

CONCLUSIONS

In this article, the gram-to-kilogram scale-up synthesis of DABPA through both the conventional batch process and the flow chemistry was examined. Firstly, the optimal reaction temperature of this thermal rearrangement was confirmed by DSC. Then we carried out a ten-gram-scale synthesis through a traditional batch process and the reaction went well. Thus a following 100-gram scale-up preparation utilizing the same conditions was tried and found huge heat was emitted when the reaction began, which not only promoted the formation of many by-products but also would bring various uncontrollable risks such as bumping. Therefore, we developed a continuous flow synthetic platform by using a microchannel reactor to achieve the synthesis of DABPA via thermal Claisen rearrangement with high efficiency and safety. The flow velocity of the reactant was screened and optimized reaction conditions were then established. The advantage of the continuous systems when compared with the conventional batch method was only a small amount of reactant was allowed to stay in the reactor which avoided the accumulation of large quantities of reaction heat thus to enhance the safety of the reaction process and reducing the formation of many byproducts. At last, kilogram scale-up synthesis of DABPA was easily accomplished after the reactant flowed past the well-run reaction system for 3h, offering an efficient strategy for the scale-up synthesis of this compound. Further improvement of this flow reaction system including changing the heating method, and linking a separation and purification system is ongoing in our laboratory. Besides, the application of this reactive functional molecule in various polymers is also under exploration by our cooperative partner.

Acknowledgments

This work was supported by the Key Research and Development Program of Shaanxi (Program No. 2019ZDLGY04-06, 2021GY-228) and Xi'an Modern Chemistry Research Institute. Besides, the author would like to thank Engineer Zheng Lv at Himile Mechanical Science & Technology (Shandong) Co., Ltd for his help in the installation of the simple continuous flow reactor.

Received : Dec.21, 2022 ; Accepted : Apr.17, 2023

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