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Green and catalyst-free synthesis of deoxyarbutin in continuous-flow†

Xiaoxuan Xie,[a] Shitian Xie,[a] Hongmiao Yao,[a] Xin Ye,[b] Zhiqun Yu*[a] and Weike Su *[ab]

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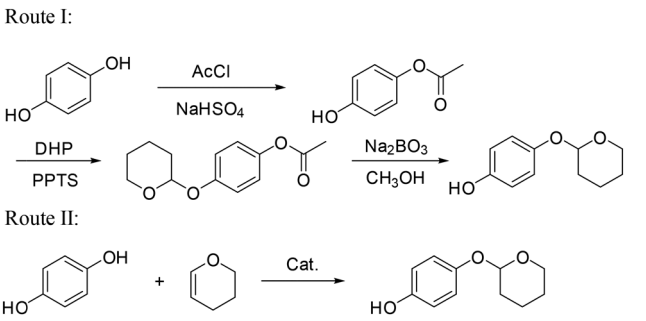
A one-step catalyst-free continuous-flow etherification protocol has been developed for the preparation of deoxyarbutin. The starting material hydroquinone was etherified with 3,4-dihydro-2*H*-pyran (DHP) to gain deoxyarbutin directly. A material recycling method was established to address the drawback of low per pass conversion which is caused by the reversible equilibrium of this reaction. The continuous-flow methodology is effective in inhibiting the double etherification side reaction to realize the facile and highly efficient preparation of deoxyarbutin.

Introduction

Deoxyarbutin is a tyrosinase inhibitor which can be used as a cosmetic additive to inhibit the formation of melanin to achieve skin lightening and shows some antitumor activity against melanoma.[1] Compared to most of the tyrosinase inhibitors (*e.g.*, hydroquinone, kojic acid, arbutin, *etc.*), deoxyarbutin has many features such as rapid and sustained skin lightening. The damage caused by deoxyarbutin to melanocytes is completely reversible within 8 weeks after a halt in topical application.[2]

There are two main synthetic routes for the preparation of deoxyarbutin (Scheme 1). Route I: hydroquinone is etherified with DHP after mono-esterification to avoid the formation of 1,4-bis((tetrahydro-2*H*-pyran-2-yl)oxy)benzene, then the ester group is hydrolyzed to obtain the final product deoxyarbutin.[3] The protection and de-protection method is usually the last resort, due to its bad atom economy and at least two more unit operations. Route II: direct etherification of hydroquinone to gain the target product deoxyarbutin.[4] This route suffers from poor selectivity, and the consecutive side reaction is hard to avoid. Since unsatisfactory reaction selectivity exists in both routes, *i.e.* esterification in route I and etherification in route II, optimizing and improving the direct mono-etherification to gain deoxyarbutin could be more effective and accessible. Therefore, we adopted route II for the synthesis of deoxyarbutin and hope to develop a highly selective and practical process. To avoid the consecutive side reaction of this simple symmetrical compound, developing a regioselective catalyst is financially unnecessary; thus we set our sights on developing a suitable reactor to solve this problem. The proposed mechanism for the reaction sequence is shown in Scheme 2.[5] The oxonium intermediate **3**, generated by protonation of DHP **2**, possessed strong electron affinity and could be attacked easily by the oxygen atom of **4**. Yet, the target compound deoxyarbutin **1** could react with **3** to form the main side product **5**. Thus, how to avoid the consecutive side reaction is the key to the study.

In the last 20 years, continuous-flow technology has been widely reported and researched in both industry and academia.[6] Compared to a traditional batch vessel, a flow reactor has many advantages such as better thermal and mass transfer, more accurate control of reaction parameters such as temperature, stoichiometry, molar ratio, pressure, and residence time, and better equimolar ratios;[7] meanwhile poor mixing can result in mixtures of the starting material, product, and overreacted product.[8] Owing to negligible back



Scheme 1 Synthetic routes of deoxyarbutin.

[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: yzq@zjut.edu.cn*

[b] *Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: pharmlab@zjut.edu.cn*

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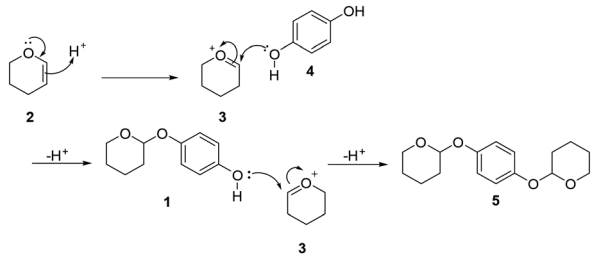


Scheme 2 Proposed mechanism for etherification.

mixing and faster mixing, continuous-flow reactors are especially suitable to be applied for improving the selectivity of processes which have consecutive side reaction problems.[9] Our team is experienced in adapting various reactions (diazotization, nitration, hydrolysis, *etc.*) from the batch process to continuous-flow[10] and we have done some works about inhibiting consecutive side reactions.[10a,b] By applying continuous-flow technology, a reaction can proceed under unconventional, more intensive reaction conditions to enhance the reaction efficiency.[10c]

We herein described a practical process for the one-step highly selective synthesis of deoxyarbutin in a continuous-flow reactor. In addition, the reaction is converted to a catalyst-free one, and the drawback of low per pass conversion was addressed with the aid of a material-recycling process, thereupon the unit consumption of the raw material was greatly reduced.

Results and discussion

Optimization of selective mono-etherification in batch

According to the literature,[4,11] acid catalysts (*e.g.*, pyridinium 4-toluenesulfonate, TsOH, HCl, $Fe_2(SO_4)_3{\cdot}xH_2O$, *etc.*) were widely used in the synthesis of **1** *via* mono-etherification of **4**. To find out the most suitable catalyst, a series of trials were made to explore the mentioned acid catalysts. As shown in Table 1, pyridinium 4-toluenesulfonate (PPTS) has the best performance under conditions of 30 °C and 4 h. It not only has the highest conversion rate, but also has slightly better reaction selectivity in our process. According to the results, catalysts with stronger acidity also bring a higher conversion rate. As shown in the presented mechanism, the acidity of the catalyst is sensitive to the reaction rate. Too strong acidity might promote hydrolysis of **1**, whereas too weak acidity makes it hard to protonate **2**, which makes it hard for hydroquinone to attack **2**. Meanwhile, the usage of a catalyst was also explored, and had hardly any effect on results from 10% mol to 100% mol; therefore 10% mol PPTS was selected as the catalyst for etherification.

Table 1 The effect of various catalysts on mono-etherification[a]

Catalyst	Conv.[b] (%)	Selectivity (%)
PPTS	36.5	97.5
36% HCl	15.5	96.5
$TsOH{\cdot}H_2O$	22.2	92.6
$Fe_2(SO_4)_3{\cdot}xH_2O$[c]	—	—
No catalyst[c]	—	—

[a] Reaction conditions: **2** (33.3 mmol), **4** (100 mmol), catalyst (3.3 mmol), 30 °C, 4 h. [b] Conversion of DHP. [c] No target compound formed.

Once the catalyst was determined, the related parameters of etherification, such as the molar ratio of **4** to **2** and reaction temperature (T), were investigated systematically in the batch method. As shown in Fig. 1(a), the mixture of **4** and **2** was stirred for 4 h at 30 °C. The reaction selectivity increased along with the increase of the usage of hydroquinone, whereas the maximum conversion occurred when the molar ratio of **4** to **2** was 9 : 1 and decayed rapidly as the usage of **4** continued to increase. This is probably due to the concentration of **4** being much higher than that of **1**, which gives **4** more opportunities to react with **2**. As the concentration of **4** continues to increase, it becomes more like a solvent than a reactant. Compared to 2-Me-THF, **4** has a weaker tendency to accept a proton; thus, the ionization of PPTS is inhibited. Finally, the effect of temperature on etherification was explored as shown in Fig. 1(b). The reaction was impeded considerably when the temperature was below −15 °C; the reaction rate rose obviously with elevated temperature, the conversion was improved (within the same reaction time of 4 h), and the selectivity of the reaction hardly decreased. It had been found experimentally that the conversion of the material increased along with the increase in reaction time until a maximum was reached. There is a reversible equilibrium in the mono-etherification, and the per pass conversion would be restricted due to the existence of this reversible equilibrium. The exploration of temperature illustrated that a temperature rise was beneficial for the reaction to shift towards the direction of a positive reaction. Fortunately, the reaction temperature has a low impact on the reaction selectivity under a considerable excess of **4** (the reaction selectivity mainly depended on the concentration effect). The major side reaction is di-etherification; it is a consecutive side reaction. The residence time distribution in the continuous flow reactor is

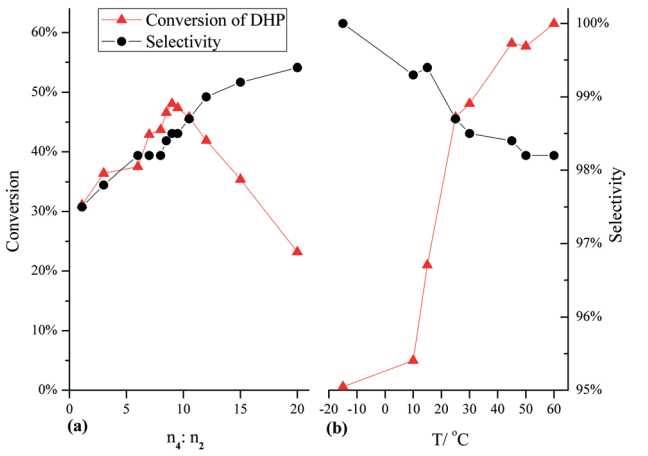
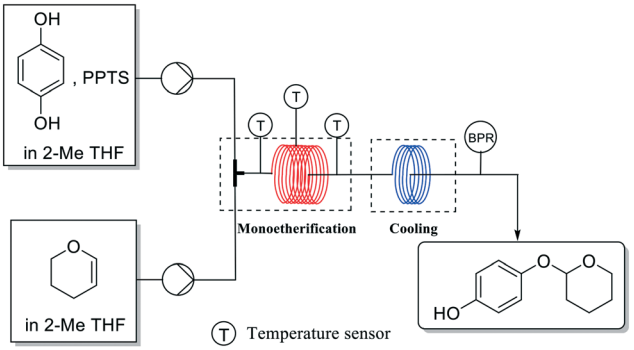


Fig. 1 The effect of related parameters on etherification.



Scheme 3 Primitive continuous-flow process for the preparation of deoxyarbutin.

narrow, therefore, the consecutive side reaction, in this case di-etherification, could be restricted.[9] In addition, the reaction temperature could be significantly increased due to the improvement of the solvent boiling point which resulted from pressurization in the continuous-flow reactor, thereby accelerating the etherification and increasing the material conversion rate. Therefore, our objective is to develop a one-step high selectivity and efficiency continuous-flow process for the synthesis of deoxyarbutin.

Initial design of the continuous-flow process

Based upon the demand, a facile continuous-flow reactor was designed. As shown in Scheme 3, two streams, **4** with PPTS (10% mol) in 2-Me-THF and **2** in 2-Me-THF, were pumped into a reacting tube (SS316L, 1.77 mm i.d., 3.18 mm o.d.) *via* a T-joint (SS316L, 1.77 mm i.d.) by two plunger metering pumps (SS316L, BOOK) respectively. The mono-etherification tube was submerged in a thermostat-controlled oil bath and several temperature sensors were embedded inside the mono-etherification tube to monitor the reaction temperature. In order to reach a relatively high reaction temperature (far beyond the boiling point of the solvent under atmospheric pressure), a back-pressure regulator (BPR) was installed in the tail of the flow reactor to pressurize the reaction system. The back pressure was set to 145 psi, and all plunger metering pumps (SS316L, BOOK) were set with a built-in automatic pressure shut-down device to prevent the reactor from overpressurizing. After achieving a 5 min residence time for etherification, the reaction mixture flowed into the collection vessel after passing through the cooling tube. A set of experiments involving the etherification temperature were conducted (Table 2), and unfortunately, the results indicated that the yield decreased with elevated temperature. Besides **5**, a new side product (a polymer of **4**) was found by HPLC-MS, whose amount significantly increased with elevated temperature. Thus, two controlled experiments were designed accordingly to find out the source of the formation of side products, which are: (I) introducing only the feed stream of **4** and PPTS (10% mol) in 2-Me-THF into the reactor and (II) introducing only the feed stream of **4** in 2-Me-THF into the reactor. Both of them were carried out under the same flow conditions as mentioned above (τ = 5 min, T = 160 °C). The results showed that the polymer side product was found in experiment I while only hydroquinone was detected in experiment II. Therefore, we could reasonably infer that PPTS played an important role in the generation of the polymer side product.

Table 2 Effect of temperature in the initial continuous-flow process

Entry	Temp. (°C)	Conv.[a] (%)	Polymer product (%)
1	100	52.3	—
2	160	30.0	18.7
3	190	22.0	62.0

[a] Conversion of DHP.

Table 3 Effect of temperature in the advanced continuous-flow process

Entry	Temp. (°C)	Conv.[a] (%)	Side products (%)
1	100	49.6	—
2	160	28.5	0.7
3	190	10.7	15.9

[a] Conversion of DHP.

Advanced method of the continuous-flow process

Considering that the presence of PPTS might lead to the formation of a considerable amount of the undesired polymer side product at high temperature, in addition, the etherification was carried out generally with the aid of protonic catalysis (Scheme 2). Thus, we thought of finding an alternative catalyst, or even better, developing a catalyst-free etherification system. As we all know, the ionization constant increases with temperature, and high temperature promotes the ionization of **4**, which might create a double advantage for etherification: the generated proton was able to catalyze the reaction; on the other hand, the phenoxy anion transformed from **4** possessing stronger nucleophilic capacity, and

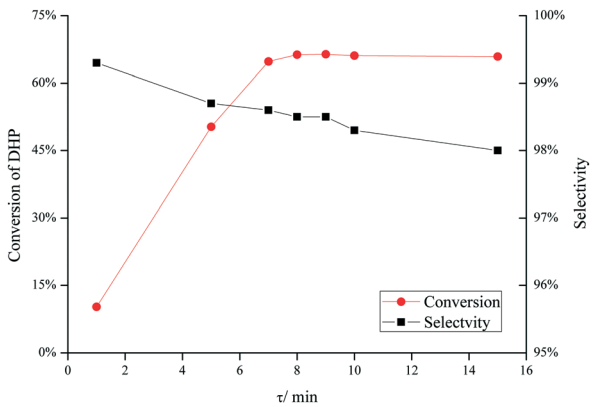
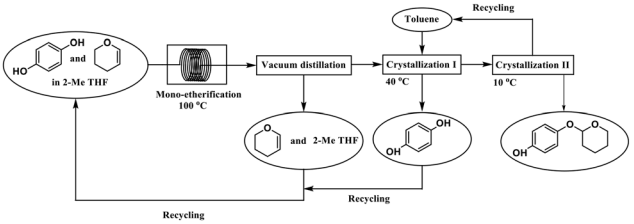


Fig. 2 Effect of τ on the yield of deoxyarbutin.

Table 4 Difference in ability of recovering hydroquinone among several solvents

Entry	Solvent	4 loss[a] (%)	Corrected yield[b] (%)
1	DCM	6.2	55.4
2	Toluene	0.6	93.0
3	*o*-Xylene	1.8	81.1
4	*m*-Xylene	1.0	88.7
5	Mesitylene	1.8	81.1

[a] Loss of 4 from recovery. [b] Corrected yield was calculated from hydroquinone and corrected on percent recovery.



Scheme 4 Process flow chart.

thus it could provide a higher reaction activity. To prove our speculation, we only prepared 4 in 2-Me-THF as the first feed stream and 2 in 2-Me-THF was introduced as the second stream. The flow rates were 1.0 mL min^{-1} and 0.3 mL min^{-1}, respectively, and the molar flow ratio of 4 to 2 was 9 : 1.

To our delight, 4 could react with 2 to obtain the target product under catalyst-free conditions. The conversion is a little less than that with the presence of PPTS. In sharp contrast, the side products decreased obviously and even disappeared almost entirely when the reaction temperature was below 160 °C (Table 3), which confirmed our speculation. With or without PPTS, the conversion decreased with elevated temperature, probably because the 2 monomer homopolymerized under the effect of acid and high temperature.[12] The conversion reached a maximum of 49.6% when T = 100 °C. The optimization of the etherification residence time (τ) was carried out and the results are shown in Fig. 2. The etherification reached equilibrium in around 8 min with a conversion of 66.3% and a selectivity of 98.5% at 100 °C. The selectivity of the reaction slightly decreased with prolonged time; we inferred that as product 1 accumulates until reaching a maximum, the consecutive side reaction becomes the dominant reaction; hence, a prolonged residence time was not favourable to the selectivity of the main reaction. Overall, we developed a one-step catalyst-free continuous-flow process for the synthesis of 1. Under the above conditions, a maximum yield of 65.3% of 1 (calculated from 2) was obtained when T = 100 °C and τ = 8 min.

Recycling process of materials

On the basis of our above-mentioned work, an advanced process had been developed which could be conducted facilely to obtain 1 directly through one-step highly selective monoetherification. Yet, a large excess of material 4 and a certain amount of unreacted 2 were wasted. To mitigate this, an idea of recycling the materials popped up.

We found that 2 has excellent solubility in most organic solvents and its boiling point is close to that of solvent 2-Me-THF, and vacuum distillation could separate them from the reaction mixture and obtain a mixture of them for recycling. Then, a series of solvents (Table 4) were tested to separate 4 and 1 in succession from the reaction system by a programmed cooling method. Toluene showed the best ability and the repeatability of results was satisfactory; the average recovery rate[13] was 99.0% and the corrected yield was 93.0%. Afterwards, the reaction system was modified to make recycling more practical (Scheme 4). Since 2 doesn't react with 4 at room temperature, we can premix 2 and 4 in a vessel, which not only saved a set of conveying pipeline and appurtenance, but also made the reuse of 2, 4 and 2-Me-THF more convenient. The recovered 2, 4 and 2-Me-THF were reused in the same process and the results showed that they had a remarkable compatibility with commercially available raw materials. Consequently, a practical process for recycling the materials was developed successfully.

To emphasize the advantage of continuous-flow synthesis, the comparison between continuous-flow technology and batch mode was summarized. As shown in Table 5, not only was the catalyst PPTS removed in the flow process, but also slightly better yield and purity were obtained within a short period of time. The reaction time was noticeably reduced which benefitted from increasing the temperature and thereby utilizing the superior mass and heat transfer of the continuous-flow system. Eventually, the high-purity 1 could be obtained directly *via* one-step catalyst-free etherification efficiently with the aid of continuous-flow methodology.

Conclusion

A continuous-flow, catalyst-free process has been described for the synthesis of deoxyarbutin from hydroquinone *via* one-step direct etherification. The reaction time was remarkably reduced to 8 min by increasing the reaction temperature and

Table 5 Comparison of etherification in different operation manners

Operation manner	Catalyst	Reaction temperature (°C)	Reaction time	Yield[a] (%)	Purity (%)
Batch	10 mol% PPTS	60	4 h	60.4	98.1
Advanced continuous-flow	No catalyst	100	8 min	65.3 (93.0)[b]	98.5

[a] Conversion was HPLC conversion of DHP, calculated from hydroquinone *via* an external standard method. [b] 65.3% is the once through yield, 93.0% is the corrected yield.

thereby taking advantage of the superior mass and heat transfer arising from the continuous-flow system. Ultimately, an efficient recycling process of material **2** and **4** was developed to address the drawback of low per pass conversion; the solvents and unreacted material could be recycled in this process. Excess **4** and unreacted **2** were recovered, the target product was separated by a programmed cooling method, and the corrected yield of the product reached 93.0% consequently. This method agrees with green chemistry principles, exhibits high efficiency and almost no waste release, and is promising for industrial application.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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13 The recovery rate is equal to recovered hydroquinone divided by unreacted hydroquinone.