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Green Synthesis of β-(3,4-Dihydroxyphenyl)lactic Acid

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A new method has been developed for the synthesis of β-(3,4-dihydroxyphenyl)lactic acid, an active ingredient for the treatment of myocardial ischemia. Pd/C catalysts were used in the key reduction reaction to replace the traditionally used toxic Zn/Hg catalysts. A significantly high product yield of 99.7 % was obtained under the optimal reaction conditions, through the use of orthogonal experimental design, when reaction temperature, catalyst (5 % Pd/C) amount and pressure were 60 ºC, 20 wt % and 1.0 MPa, respectively.

Key Words: β-(3,4-Dihydroxyphenyl)lactic acid, Pd/C catalyst, Reduction, Hydrogenation, Orthogonal experimental design, Green synthesis.

INTRODUCTION

β-(3,4-Dihydroxyphenyl)lactic acid, a water-soluble compound originally derived from Traditional Chinese Medicine Salvia miltiorrhiza (Danshen), has been regarded as the active ingredient for the treatment of myocardial ischemia[1]. The structure is shown in Fig. 1. Owing to its instability, it often exists in the form of sodium lactate. Previous studies have demonstrated its effects on other related conditions, including the dilation of blood vessels[1], the increase in coronary blood flow[2] and antithrombotic[2,3]. Therefore, great effort has been made for the chemical synthesis of β-(3,4-dihydroxyphenyl)-lactic acid[4,5] and its derivatives[6-8]. For example, Xue *et al.*[9] studied the chemical synthesis of β-(3,4-dihydroxyphenyl)-lactic acid through the Clemmensen reduction of β-(3,4-dihydroxyphenyl)pyruvic acid. This reaction was also examined by other researchers with total yields in the range of 20-30 %[10-12]. In addition, Tong *et al.*[13] used $NaBH_4$ in the reduction reaction by without pollution and after a 6-step process a total yield of 48.4 % was obtained. Recently, Zhang *et al.*[4] employed a microwave-assisted heating method on this synthetic process with an aim to improve the yield.

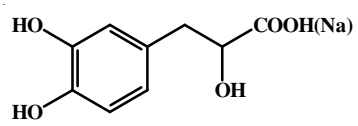


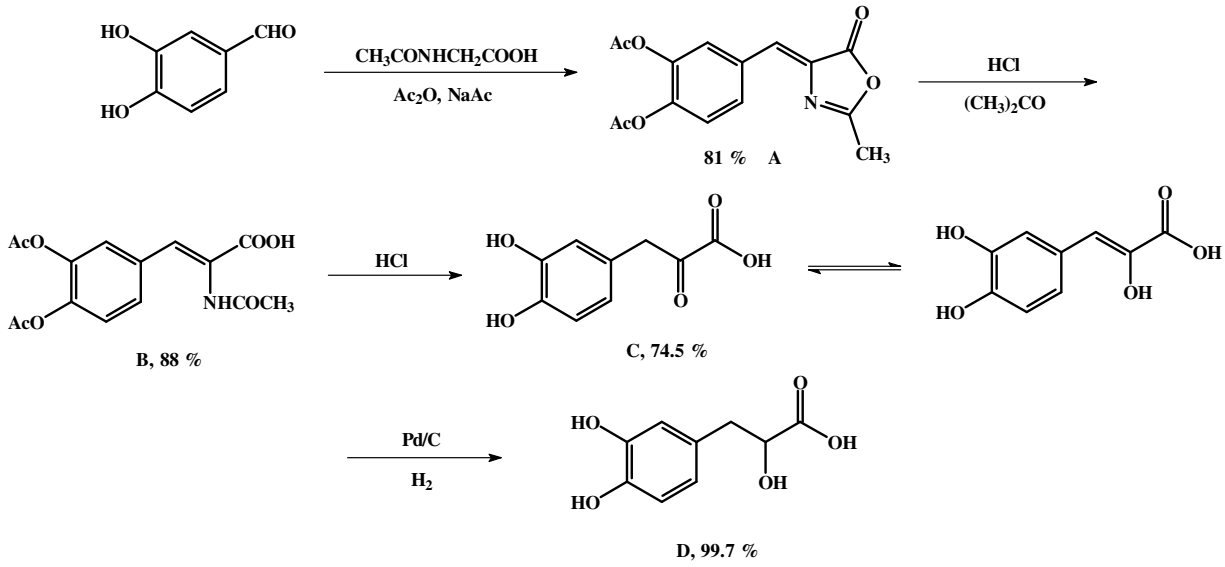
Fig. 1. Sodium β-(3,4-dihydroxyphenyl)lactate

However, all processes described above have some limitations, especially related to environmental issues. Firstly, the use of Zn/Hg catalysts causes major problems for the treatment of wastewater containing mercuric salt. Secondly, large volumes of solvent are required during the process while the total yield is relatively low. Although the total yield has been improved with microwave heating, the development of this new process is still at the early stage. The aim of the present study was to address those issues by replacing the toxic Zn/Hg catalysts with Pd/C catalysts which have been commonly used for hydrogenation[14], reducing solvent consumption and significantly improving the total yield, in order to develop a greener process for the synthesis of β-(3,4-dihydroxyphenyl)-lactic acid.

EXPERIMENTAL

3,4-Dihydroxybenzaldehyde (C.P.) was purchased from Guangxi Chemicals Import and Export Ltd. 5 % Pd/C was obtained by Baoji Ruike Nonferrous Metals. β-(3,4-Dihydroxyphenyl)lactic acid (standard sample, Batch No. 110855-200506) was supplied by China National Institute for Food and Drug Control (NIFDC). An HPLC (Agilent 1100) and a NMR (INOVA-400 MHz, Varian) were used for chemical analysis. The synthetic route is shown in **Scheme-I**.

Preparation of 2-methyl-4-(3,4-acetoxybenzylene) oxazol-5-ones: A mixture of 3,4-dihydroxybenzaldehyde (55.2 g, 0.4 mol), N-acylglycine (56.6 g, 0.5 mol) and anhydrous



Scheme-I: Synthesis route

NaOAc (42.6 g, 0.5 mol) in 205 mL Ac_2O was heated and stirred at 80 ºC for 4 h and then at 100 ºC for 1 h. When cooling to room temperature 200 mL ice-water was added and the mixture was stirred for until yellow crystals formed. It was then filtered, washed with cold water (2 mL × 30 mL) and dried under vacuum to produce the light yellow crystal product A (97.0 g, m.p. 161.0-161.4 ºC) with a yield of 80.9 %.

Preparation of α-acetylamino-β-(3,4-diacetoxyphenyl)acrylic acid: A mixture of A (50.17 g, 0.16 mol), acetone (184 mL) and water (184 mL) was slowly heated to reflux for 4 h. After the mixture of reaction decolorized with the appropriate amount of active carbon, it was cooled to 5-10 ºC for complete crystallisation. After filtered by suction, washed with cool water and dried under vacuum, yellow crystal powder B was obtained (45.6 g, m.p. 188.9-189.1 ºC) with a yield of 88 %.

Preparation of β-(3,4-Dihydroxyphenyl)pyruvic acid: A mixture of B (51.4 g, 0.16 mol) in 1 N HCl (500 mL) was heated to reflux while stirring for 8 h. After the mixture of reaction decolorized with the appropriate amount of active carbon, it was filtrated by suction before cooling. After the filtrate was concentrated under vacuum for crystal precipitation, it was cooled with ice-water bath so as to crystallize completely. The resulting crystal was washed with ice-water, dried under vacuum and recrystallized from water to form intermediate compound C as yellowish-white crystals (23.4 g, m.p. 191.2-191.6 ºC) with a yield of 74.5%. ^{1}H NMR (400 MHz, DMSO) δ ppm: 6.22(s, 1H), 6.67(d, J = 8.4Hz, 1H), 6.90 (dd, J = 8 Hz, J = 2 Hz, 1H), 7.31 (d, J = 2 Hz, 1H), 8.78 (s, 1H), 8.93 (s, 1H), 9.07(s, 1H).

Synthesis of β-(3,4-dihydroxyphenyl)lactic acid: Intermediate compound **C**, 5 % Pd-C (amount given in Table-1) and ethanol (160 mL) were mixed in a stirred autoclave. After air was replaced with N_2, H_2 was introduced to replace N_2 in the reaction system, which was then heated up to desired temperature. When H_2 was exhausted, the reaction mixture was filtered by suction. After the filtrate was concentrated under vacuum, slight yellow oil-like product was obtained and the product yield was determined.

RESULTS AND DISCUSSION

The main focus of this study is on the hydrogenation step for forming D, β-(3,4-dihydroxyphenyl)lactic acid. The reaction conditions for hydrogenation were initially examined by varying reaction temperature, amount of catalyst (5 % Pd/C) as weight percentage of reactants and reaction pressure, to determine the variable range. Based on the initial results, an orthogonal experimental design was carried out and the three experimental factors at three levels are shown in Table-1.

TABLE-1
EXPERIMENTAL FACTORS AND LEVELS

Level	Factor A temperature (ºC)	Factor B 5 % Pd/C (wt/%)	Factor C pressure (MPa)
1	10	5	0.1
2	30	10	0.5
3	60	20	1.0

The orthogonal test programs, $L_9(3^3)$ and test results are summarized in Table-2 and the ANOVA results are shown in Table-3.

As can be seen from results in Tables 2 and 3, all three factors examined in the selected ranges had significant effects on the hydrogenation yield. Furthermore, the R values indicated that the influence to the hydrogenation yield of the

TABLE-2
ORTHOGONAL EXPERIMENT DESIGN AND RESULTS

Trial #	A	B	C	Yield (%)
1	1	1	1	72.7
2	1	2	2	79.7
3	1	3	3	89.3
4	2	1	2	74.5
5	2	2	3	90.4
6	2	3	1	84.5
7	3	1	3	90.6
8	3	2	1	87.7
9	3	3	2	93.8
R_1	R_1^A = 80.6	R_1^B = 79.3	R_1^C = 81.6	–
R_2	R_2^A = 83.1	R_2^B = 86.0	R_2^C = 82.7	–
R_3	R_3^A = 90.7	R_3^B = 89.2	R_3^C = 90.1	–
R	10.1	9.9	8.5	–

Table-3
Analysis of variance (ANOVA) results

Source	Sum of squares	Degree of freedom	Mean square	F-Ratio
A	166.5	2	83.3	32.0
B	153.7	2	76.8	29.5
C	128.0	2	64.0	24.6
Error	5.2	2	2.6	–

target compound decreases in the order of A > C > B, *i.e.*, the reaction temperature was the most significant factor. It was also shown in the nine experimental runs that the maximum yield (93.8 %) of the compound D was obtained under the experimental condition of $A_3B_3C_2$. Based on the orthogonal experimental design results, further optimization was carried out for a hydrogenation yield of 99.7 %, indicating the optimal experimental condition being $A_3B_3C_3$. In other words, the maximum hydrogenation yield of β-(3,4-dihydroxyphenyl) lactic acid was obtained when reaction temperature, catalyst (5 % Pd/C) amount and pressure were 60 ºC, 20 wt % and 1.0 MPa, respectively. Furthermore, the reaction time was reduced to 20 h in $A_3B_3C_3$, which was significantly shorter than that reported (48 h) in the literature[8].

The obtained compound was further confirmed by HPLC (Zorbax SB-C_{18} 4.6 mm × 150 mm, 5.0 μm; 280 nm; 0.8 mL min^{-1}; methanol: 0.5 % acetic acid = 10:90); the standard sample (99.8 % purity) RT was 9.886 min peak while the synthetic target compound RT was 9.927 min (97.6 % purity). It was also confirmed by ^{1}H NMR (400 MHz, DMSO) δ ppm: 2.74(dd, *J*=13.6 Hz, *J*=5.2 Hz, 1H), 4.12(dd, *J*=7.6 Hz, *J*=5.4 Hz, 1H), 6.41(d, *J*=8.0 Hz, *J*=1.9Hz, 1H), 6.59(d, *J*=8.4 Hz, 1H), 6.72(d, *J*=1.9Hz, 1H), 7.68(brs, 3H).

Conclusion

A greener method has been developed in this study by using Pd/C catalysts to replace toxic Zn/Hg catalysts for the synthesis of β-(3,4-dihydroxyphenyl)lactic acid. A significantly high hydrogenation yield of 99.7 % was obtained under the optimal reaction conditions through the use of orthogonal experimental design. The reaction time was also reduced significantly compared with the literature data (20 h *versus* 48 h).

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