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Synthesis of β-(4-chlorophenyl) lactic acid

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Abstract. β-(4-chlorophenyl)lactic acid was synthetized via four steps of reaction, knoevenagel condensation, oxazolone ring-opening, hydrolysis and clemmensen reduction, staring from commercially available compound 4-chlorobenzaldehyde. β-(4-chlorophenyl) lactic acid and its mid-products were identified with ^{1}H NMR, ^{13}C NMR and MS. The spectra and physical constants were concordant with the corresponding structures and properties. The synthetic route we used has the advantages of abundant materials, simple process, mild reaction, without special equipments, much lower costs, ect.

Keywords: β-(4-chlorophenyl) lactic acid; Danshensu derivatives; Synthesis.

1. Introduction

Tanshinol, known as D-(+)-β-(3,4-dihydroxyphenyl) lactic acid, is the main water-soluble component of Salvia miltiorrhiza Bge. [1] Results of pharmacologic experimental study showed that Tanshinol has the function of protective effect on myocardial isch, preventing atherosclerosis, protect liver, anti-bacterial and anti-inflammatory, antitumor and antithrombotic. [2-5] However, the ortho phenolic hydroxyl groups in the structure of Danshensu are easily oxidized, and the source of Danshen is limited. The content of Danshensu in Danshen is relatively low, and the extraction and separation steps are relatively complex.

Therefore, it has certain limitations in extracting danshensu from Salvia miltiorrhiza plants for research or medicinal use. β-(4-chlorophenyl) lactic acid was synthetized via four steps of reaction, knoevenagel condensation, oxazolone ring-opening, hydrolysis and clemmensen reduction, staring from commercially available compound 4-chlorobenzaldehyde (As shown in Figure 1). This study lays the foundation for the structure-activity relationship and pharmacological mechanism of danshensu to develop new drugs.

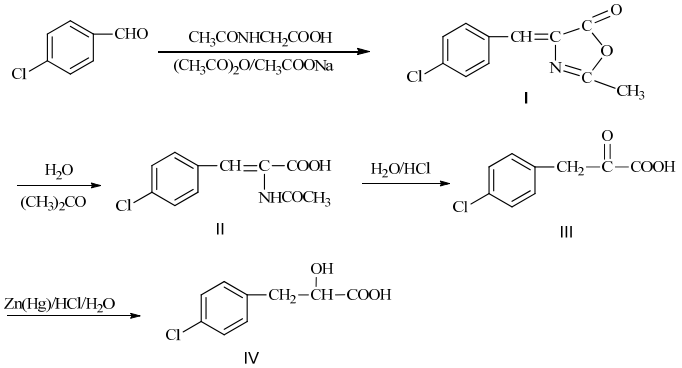

Figure 1. Synthetic route of β-(4-chlorophenyl) lactic acid

2. Organization of the Text

2.1 Instrument and Reagent

Varian Inova-400MHz nuclear magnetic resonance instrument (DMSO-d6 as solvent, TMS as internal standard); HP 1100 mass spectrometer. All reagents used are analytical or chemical pure.

2.2 Preparation of Acetoglycocol

Add 10.1 g (0.134 mol) of glycine and 27 mL (0.472 mol) of acetic acid to a 250 mL three necked bottle equipped with a stirrer, stir, and add 14 mL (15.1 g, 0.128 mol) of acetic anhydride dropwise in a 30℃water bath [6]. The dropwise addition is completed within 30 minutes. Continuous stirred reactor for 4 hours in 55-60℃water bath, and the reaction solution is fully cooled. Filter, sediment, washed with water, and dry to obtain 14.9 g of white solid, with a yield of 95.5%, mp 206-208 ℃ (Reference [7] mp 204-206℃).

2.3 Preparation of Compound I

Add 6.0 g (0.051mol) of acetoglycocol, 5.9 g (0.042mol) of 4-chlorobenzaldehyde, 4.2 g (0.51 mol) of newly melted Sodium acetate anhydrous, and 200 mL of acetic anhydride to the reaction bottle equipped with a thermometer and stirrer. Stir evenly and slowly raise the temperature. The solid reactants gradually dissolve, and continue to stir at around 95℃ for reaction. After the reaction is completed, 200 mL of cold water is poured into the reaction solution [8] and put in the refrigerator overnight. Filtered, the precipitate iss washed with dilute ethanol, and dry to obtain 7.7g of yellow solid compound I with a yield of 82.8%, mp 144-146 ℃.

MS (ESI): found for $C_{11}H_8O_2NCl$ $[M-H+CH_3OH]^-$ 252; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.401~2.515 (s, 3H, CH_3), 7.567~7.585 (d, J = 7.2 Hz, 2H, Ph-H-2, Ph-H-6), 8.188~8.201 (d, J = 8.8 Hz, 2H, Ph-H-3, Ph-H-5), 7.239 (s, H, =CH) ; ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 15.585 (CH_3), 128.401 (Ph-C-1), 129.190 (Ph-C-2, Ph-C-6), 133.661 (Ph-C-3, Ph-C-5), 135.862 (Ph-C-4), 133.243 (C-N), 167.354 (O=C, N=C), 132.150 (=CH).

2.4 Preparation of Compound II

Add 8.0g(0.0334mol) of compound I, 100ml acetone, 100ml distilled water in a 250ml round- bottom flask. Stir well and then refluxing by raising temperature slowly. Filter while hot after the reaction is completed. The filtrate is naturally cooled and left in a refrigerator overnight. Filtered, precipitate was washed with ice water, and dry to obtain 6.3 g of yellow solid compound II with a yield of 72.8%, mp 226-228℃.

MS (ESI): found for $C_{11}H_{10}NO_3Cl$ $[M-H]^-$ 238 ; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.762 (s, 1H, COOH), 9.496 (s, 1H, NH), 7.196 (s, 1H, =CH), 7.611~7.632 (d, J = 8.4 Hz, 2H, Ph-H-3, Ph-H-5), 7.459~7.472 (d, J = 5.2 Hz, 2H, Ph-H-2, Ph-H-6), 1.983 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 22.766 (CH_3), 169.351 (NHCO), 128.090 (Ph-C-1), 128.750 (Ph-C-2, Ph-C-6), 131.536 (Ph-C-3, Ph-C-5), 132.917 (Ph-C-4), 166.459 (COOH), 133.668 (=C), 129.638 (=CH) .

2.5 Preparation of Compound III

Add 3.5 g (0.0146 mol) of compound II and 120 mL of 9% aqueous HCl solution to a reaction flask equipped with a stirrer, and reflux [9]. After the reaction is completed, cool naturally and placed the reaction solution in the refrigerator overnight. Filtered, precipitate was washed with ice water, and dry to obtain 2.2 g of brown solid compound III with a yield of 75.9%, mp 188-190 ℃.

MS (ESI): found for $C_9H_7O_3Cl$ $[M-H]^-$ 197; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.306 (s, 1H, COOH), 6.4 (s, 1H, NH), 9.480 (s, 1H, OH), 6.401 (s, 1H, =CH), 7.773~7.794 (d, J = 8.4 Hz, 2H, Ph-H-3, Ph-H-5), 7.393~7.415 (d, J = 8.8 Hz, 2H, Ph-H-2, Ph-H-6); ^{13}C-NMR (100 MHz, DMSO-

d_6) δ: 108.337 (=CH), 131.558 (Ph-C-1), 128.507 (Ph-C-2, Ph-C-6), 131.004 (Ph-C-3, Ph-C-5), 142.663 (Ph-C-4), 166.315 (COOH), 134.116 (=C-OH).

2.6 Preparation of Compound IV

Add 3.0 g(0.0151 mol) of compound III, 13.4 g a newly prepared zinc amalgam, and aqueous HCl solution to a reaction bottle equipped with a thermometer and an agitator and mix well. Slowly heating up, the solid gradually dissolves, and the liquid surface is in the shape of a fountain, continuing to reflux. After the reaction is completed, it is filtered while it is hot, and the zinc powder that has not been reacted is filtered. The filtrate is naturally cooled, decompressurized, concentrated, and precipitated. And then the precipitate is washed with ice water, and dry to obtain 1.6 g white foam solid compound IV, yield 52.8%, mp 80~82℃.

MS (ESI): found for $C_9H_9O_3Cl$ $[M-H]^-$ 199(As shown in Figure 2); ^{1}H-NMR (400 MHz, DMSO-d_6) δ:11~14 (s, 1H, COOH), 7.328~7.317 (d, J = 4.4 Hz, 2H, Ph-H-3, Ph-H-5), 7.306~7.311 (d, J = 2.0 Hz, 2H, Ph-H-2, Ph-H-6), 5.1 (s, 1H, OH), 4.120~4.152 (dd, J = 4.8, 4.4 Hz, 1H, CH), 2.786~2.964 (dd, J = 8.4, 9.2, 1Hz, 1H, CH_2), 2.509~2.786 (dd, J = 2.4, 5.6 Hz, 1H, CH_2)(As shown in Figure 3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 39.381 (CH_2), 70.949 (CHOH), 131.027 (Ph-C-1), 128.052 (Ph-C-2, Ph-C-6), 131.467 (Ph-C-3, Ph-C-5), 137.3577 (Ph-C-4), 175.241 (COOH) (As shown in Figure 4).

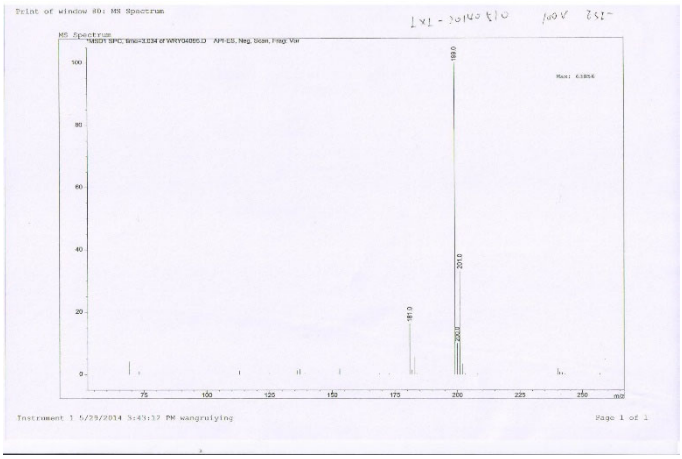

Figure 2. MS of Compound IV

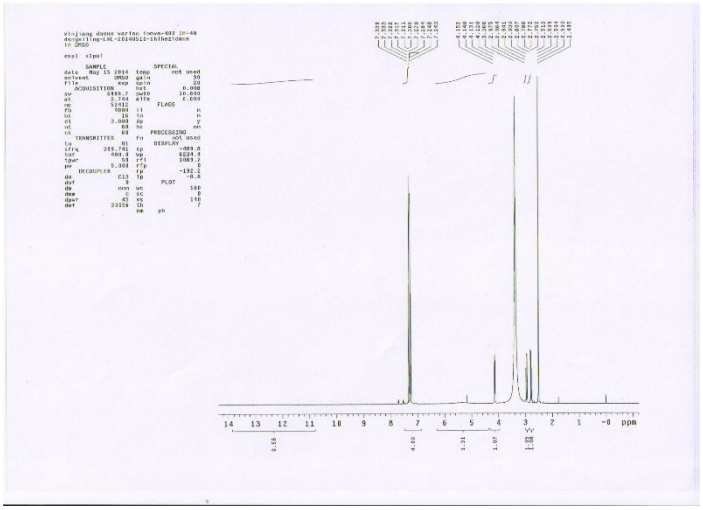

Figure 3. ^{1}H NMR of Compound IV

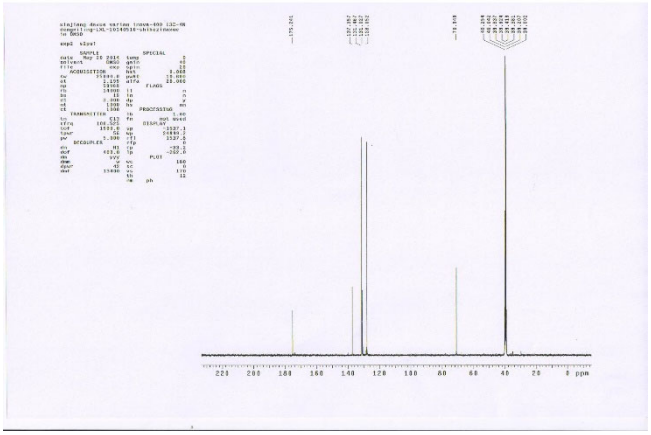

Figure 4. ^{13}C NMR of Compound IV

2.7 Results and discussion

The results indicate that most reaction yields are above 50%, the structure of the compound I-IV has been confirmed with MS, ^{1}H-NMR and ^{13}C-NMR.

3. Conclusion

The synthetic route we used has the advantages of abundant materials, simple process, mild reaction, without special equipments, much lower costs, ect. The subject mainly applies clemmensen reduction reaction to complete the synthesis of the target compound, explored the reaction conditions and synthesis process, completed the synthesis of a danshensu derivative. This has laid a certain foundation for further research on the pharmacological effects and structure-activity relationship of danshensu and its derivatives.

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