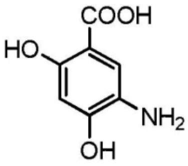
METHOD FOR SYNTHESIZING 5-AMINO-2,4-DIHYDROXYBENZOIC ACID

Field of the Invention

The present invention relates to a method for synthesizing 5-amino-2,4-dihydroxybenzoic acid (DHBA), a novel AB-type monomer for modified polyp-phenylene benzodioxazole (PBO).

Background to the Invention

The 5-amino-2,4-DHBA, as depicted in formula (I), serves not only as a novel AB-type monomer for modified PBO, but is also widely utilized in industries including dyes and pharmaceuticals.



(I)

At present, the main synthesis methods of AB-type monomer for modified PBO are as follows.

(1) 5-nitro-2,4-dihydroxybenzaldehyde is used as raw material, and the target product is prepared by oxidation and reduction (Claudio Zambaldo, Kalyan K. Sadhu, Ganesan Karthikeyan, Sofia Barluenga, Jean-Pierre Daguer, Nicolas Winssinger, Selective affinity-based probe for oncogenickinases suitable for live cell imaging [J], Chemical Science, 2013, 4: 1988-2092.). However, raw materials are expensive, post-processing is difficult and it is not easy to industrial production.

(2) 2,4-DHBA is used as a raw material, 5-amino-2,4-DHBA is prepared by diazo coupling and reduction reaction (He Weiwei. Synthesis of new hydroxyl-modified benzoxazole polymer monomers and exploration of resin fibers [D], Hangzhou: Zhejiang University of Technology, 2017: 14-30.). However, it has some shortcomings including long reaction time, difficult product separation, low purity and poor industrial production capacity.

In view of the above synthesis of 5-amino-2,4-DHBA, through groping, a new synthesis method which is easy to realize in industry and more reasonable is provided.

Statement of Invention

The present invention aims to provide an industrially feasible method for preparing high-purity 5-amino-2,4-DHBA, which has easily obtained raw materials, short reaction time, simple post-treatment, high atomic utilization rate, high yield and high purity.

The technical solutions of the present invention are as follows.

A method for synthesizing 5-amino-2,4-DHBA includes the steps of:

(1) using resorcinol as a raw material to obtain 2,4-DHBA through Koble-Schmitt reaction;

(2) nitrating 2,4-DHBA to obtain 5-nitro-2,4-DHBA; and

(3) reducing 5-nitro-2,4-DHBA to obtain a product 5-amino-2,4-DHBA.

Specifically, the method for synthesizing 5-amino-2,4-DHBA includes the steps of:

(1) mixing resorcinol, alkali and solvent water, introducing CO_2, raising the temperature to 40-120℃ and reacting for 2-7 h, and post-treating the reaction liquid to obtain 2,4-DHBA;

a molar ratio of the resorcinol to the alkali is 1:1 to 10, preferably from 1:2 to 7, more preferably from 1:4 to 6;

a volume dosage of the solvent water is 10-15 mL/g based on a mass of resorcinol;

the alkali may be any strong alkali, including sodium bicarbonate or potassium bicarbonate; and

the post-treatment method includes the steps of: after completion of the reaction, cooling the reaction liquid to room temperature (20-30℃), stopping the introduction of CO_2, filtering, adjusting the pH of a filtrate with concentrated hydrochloric acid (36-38 wt%) to 1, precipitating a solid, cooling with ice water and suction filtering to obtain a crude product, recrystallizing and purifying the crude product with distilled water, and drying the purified solid (120℃) to obtain 2,4-DHBA; and

(2) dissolving 2,4-DHBA in an organic solvent, dropwise adding concentrated nitric acid (68 wt%, recommended dropwise adding time is 2-10 min), reacting at 20-75℃ (preferably 35-50℃) for 1-7 h (preferably 3-5 h) after dropwise, and post-treating the reaction liquid to obtain 5-nitro-2,4-DHBA;

a molar ratio of 2,4-DHBA to the nitric acid is from 1:1 to 6, preferably from 1:1 to 3;

the organic solvent is acetonitrile or acetic acid, and a volume dosage of the organic solvent is 5-15 mL/g based on a mass of 2,4-DHBA;

the nitrification reaction is an exothermic reaction, too fast dropping of nitric acid will cause local overheating, increase the occurrence of side reactions, and cause the decrease of product purity, which is not conducive to industrial application; and

the post-treatment method includes the steps of: pouring the reaction liquid into a beaker filled with distilled water or crushed ice after completion of the reaction, quenching the reaction to precipitate a solid, filtering, and drying a filter cake to obtain 5-nitro-2,4-DHBA; and

(3) mixing 5-nitro-2,4-DHBA, palladium carbon and solvent, dropwise adding hydrazine hydrate (recommended dropwise adding time is 10-35 min), reacting at 40-85℃ (preferably 60-80℃) for 1-6 h (preferably 3-5 h) after dropwise, and post-treating the reaction solution to obtain a product 5-amino-2,4-DHBA;

a molar ratio of 5-nitro-2,4-DHBA to the hydrazine hydrate is from 1:1 to 10;

a mass ratio of the 5-nitro-2,4-DHBA to the palladium carbon is 1:0.02-0.1, and a content of palladium (Pd) in the palladium carbon is 5-10 wt%;

the solvent is methanol, ethanol or tetrahydrofuran, preferably ethanol;

a volume dosage of the solvent is 10-20 mL/g based on a mass of 5-nitro-2,4-DHBA; and

the post-treatment method includes the steps of: after completion of the reaction, filtering the reaction solution while the reaction solution is hot, cooling a filtrate in an ice water bath, adding stannous chloride and concentrated hydrochloric acid, standing for 5-6 h, suction filtering, and drying a filter cake to obtain a product 5-amino-2,4-DHBA; a mass ratio of stannous chloride to 5-nitro-2,4-DHBA is 0.01-0.03: 1, preferably 0.02-0.025: 1; and a volume dosage of the concentrated hydrochloric acid is 10-40 mL/g, preferably 10-25 mL/g, based on a mass of 5-nitro-2,4-DHBA.

Compared with the related art, the present invention has the advantages of easy control of reaction process parameters, easy obtaining of raw materials, short reaction time, simple post-treatment, high atomic utilization rate, high purity and high industrial feasibility.

Detailed Description

The present invention will be further described below with reference to specific examples, but the scope of protection of the present invention is not limited thereto.

Example 1

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g (0.1 mol) of resorcinol, 42 g (0.5 mol) of sodium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, the reaction was refluxed for 3 h, the heating was stopped, cooled to 40°C, the CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered and filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, recrystallized with distilled water, and the filter cake was oven dried at 120°C to obtain a white product. The mass fraction was 98.50% analyzed by high performance liquid chromatography (HPLC), and the yield was 64% calculated by resorcinol.

FT-IR (KBr, cm^{-1}): 3373.97 (s), 1668.12 (s), 1577.33 (s), 1382.68 (s), 1310.34 (s), 805.92 (s), 551.52 (s).

ESI-MS: $[M-H]^+$ = 154.1.

In a 250 mL four-necked flask equipped with a thermometer, 7.5 g (0.05 mol) of 2,4-DHBA, 60 mL of acetonitrile were sequentially added, 8 mL of concentrated nitric acid (containing 0.12 mol of nitric acid) was added dropwise, and the temperature was controlled by stirring at 35-50°C. The reaction was stopped for 3.5 hours, and the reaction solution was poured into a beaker containing 300 mL of distilled water or 100 g of crushed ice to quench the reaction.

FT-IR (KBr, cm^{-1}): 3225.4 (s), 3092.2 (s), 1668.3 (s), 1632.5 (s), 1532.6 (s), 1314.3 (s), 870.6 (s).

^1H-NMR (DMSO, δ, ppm): 12.14 (H, s,-COOH), 8.82 (H, s,-OH), 5.61 (H, s,-OH), 4.47 (2H, s, ArH).

ESI-MS: $[M-H]^+$ = 198

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g (0.02 mol) of 5-nitro-2,4-DHBA, 0.2 g of Pd/C catalyst, 60 mL of ethanol were sequentially added, 7 mL (0.14 mol) of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, and heated to reflux temperature for 3 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction was 95.20% analyzed by HPLC, and the yield was 63% calculated by 5-nitro-2,4-DHBA.

FT-IR (KBr, cm^{-1}): 2957.1 (s), 2577.4 (s), 1666.5 (s), 1603.7 (s), 1501.5 (s), 1443.8 (s), 1381.5 (s), 1264.5 (s).

^1H-NMR (DMSO, δ, ppm): 11.69 (H, s,-COOH), 11.05 (H, s,-OH), 8.82 (H, s,-OH), 6.63 (H, s, ArH), 6.59 (H, s, ArH). 1.26 (2H, s,-NH_2).

ESI-MS: $[M-H]^+$ = 168.0

2,4-DHBA, 5-nitro-2,4-DHBA and 5-amino-2,4-DHBA HPLC analysis conditions: octadecylsilyl (ODS) C^{18} column, 6.0 × 150 mm, mobile phase: acetonitrile/water = 50/50 (V/V), detection wavelength 254 nm, and flow rate 1.0 ml/min.

Examples 2-6

Examples 2-6 followed the same operational procedures as Example 1, with different parameters selected within the ranges specified by the present invention for the experiments. It was observed that under these process conditions, the purity of 2,4-DHBA, 5-nitro-2,4-DHBA, and 5-amino-2,4-DHBA hydrochloride all exceeded 86%. Additionally, the net yields of 2,4-DHBA, 5-nitro-2,4-DHBA, and 5-amino-2,4-DHBA products were above 44%, 19%, and 39%, respectively. These results demonstrate their applicability for industrial synthesis of 2,4-DHBA, 5-nitro-2,4-DHBA, and 5-amino-2,4-DHBA.

Example 2

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g of resorcinol, 42 g of sodium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, the reaction was refluxed for 4 h, the heating was stopped, cooled to 40°C, the CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, which was recrystallized with distilled water, and the filter cake was dried at 120°C to obtain a white product. The mass fraction was 96.23% analyzed by HPLC, and the yield was 50.84% by resorcinol.

In a 250 mL four-necked flask with a thermometer and a spherical condenser tube, 7.5 g of 2,4-DHBA, 60 mL of acetic acid were sequentially added, 8 mL of concentrated nitric acid was added dropwise, and the temperature was controlled by stirring at 40℃ for 1.5 h. After the reaction was completed, the reaction solution was poured into 300 mL of distilled water or 100 g of crushed ice to quench the reaction and precipitate the product, filtered, and the filter cake was dried and ground to obtain a light yellow filter cake. The mass fraction was 94.91% analyzed by HPLC, and the yield was 19.25% by 2,4-DHBA.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g of 5-nitro-2,4-DHBA, 0.2 g of Pd/C catalyst, 60 mL of methanol were sequentially added, 7 mL of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, heated to reflux temperature for 2 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction was 86.76% analyzed by HPLC, and the yield was 39.19% calculated by 5-nitro-2,4-DHBA.

Example 3

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g of resorcinol, 45 g of potassium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, and the reaction was refluxed for 4 h to stop heating, cooled to 40°C. The CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered and filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, recrystallized with distilled water, and the filter cake was dried at 120°C to obtain a white product. The mass fraction was 95.20% analyzed by HPLC, and the yield was 44.78% calculated by resorcinol.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 7.5 g of 2,4-DHBA, 60 mL of acetonitrile were sequentially added, 8 mL of concentrated nitric acid was added dropwise, and the temperature was controlled by stirring at 40℃ for 4 hours. After the reaction was completed, the reaction solution was poured into 300 mL of distilled water or 100 g of crushed ice to quench the reaction and precipitate the product, filtered, and the filter cake was dried and ground to obtain a light yellow solid. The mass fraction was 96.38% analyzed by HPLC, and the yield was 51.30% by 2,4-DHBA.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g of 5-nitro-2,4-DHBA, 0.3 g of Pd/C catalyst, 60 mL of ethanol were sequentially added, 7 mL of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, heated to reflux temperature for 2 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction was 92.49% analyzed by HPLC, and the yield was 39.58% calculated by 5-nitro-2,4-DHBA.

Example 4

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g of resorcinol, 25.2 g of sodium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, the reaction was refluxed for 4 h, the heating was stopped, cooled to 40°C, the CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, which was recrystallized with distilled water, and the filter cake was oven dried at 120°C to obtain a white product, the mass fraction was 92.49% analyzed by HPLC, and the yield was 51.38% by resorcinol.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 7.5 g of 2,4-DHBA, 60 mL of acetonitrile were sequentially added, 8 mL of concentrated nitric acid was added dropwise, and the temperature was controlled by stirring at 40℃ for 2 h. After the reaction was completed, the reaction solution was poured into 300 mL of distilled water or 100 g of crushed ice to quench the reaction and precipitate the product, filtered, and the filter cake was dried and ground to obtain a light yellow solid. The mass fraction was 92.38% analyzed by HPLC, and the yield was 30.38% by 2,4-DHBA.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g of 5-nitro-2,4-DHBA, 0.28 g of Pd/C catalyst, 60 mL of ethanol were sequentially added, 7 mL of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, heated to reflux temperature for 2 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction was 97.57% analyzed by HPLC, and the yield was 59.89% calculated by 5-nitro-2,4-DHBA.

Example 5

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g of resorcinol, 33.6 g of sodium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, and the reaction was refluxed for 4 h to stop heating, cooled to 40°C. The CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered and filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, recrystallized with distilled water, and the filter cake was dried at 120°C to obtain a white product. The mass fraction was 96.15% analyzed by HPLC, and the yield was 50.98% calculated by resorcinol.

In a 250 mL four-necked flask with a thermometer and a spherical condenser tube, 7.5 g of 2,4-DHBA, 60 mL of acetonitrile were sequentially added, 8 mL of concentrated nitric acid was added dropwise, and the temperature was controlled by stirring at 40℃ for 2.5 h. After the reaction was completed, the reaction solution was poured into 300 mL of distilled water or 100 g of crushed ice to quench the reaction and precipitate the product, filtered, and the filter cake was dried and ground to obtain a light yellow solid. The mass fraction was 98.22% analyzed by HPLC, and the yield was 39.76% by 2,4-DHBA.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g of 5-nitro-2,4-DHBA, 0.28 g of Pd/C catalyst, 60 mL of ethanol were sequentially added, 8.2 mL of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, heated to reflux temperature for 2 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction was 97.57%

analyzed by HPLC, and the yield was 63.89% calculated by 5-nitro-2,4-DHBA.

Example 6

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 11.0 g of resorcinol, 25.2 g of sodium bicarbonate, 120 mL of distilled water were sequentially added, CO_2 was stirred and heated to 100°C, the reaction was refluxed for 5 h, the heating was stopped, cooled to 40°C, the CO_2 was stopped and further cooled to room temperature, and the precipitate was filtered off. Concentrated hydrochloric acid was added dropwise to the filtrate under stirring until the pH of the reaction solution was 1. At this time, 2,4-DHBA precipitated in the filtrate, cooled with ice water and filtered by suction to obtain a crude product, which was recrystallized with distilled water, and the filter cake was oven dried at 120°C to obtain a white product, the mass fraction was 95.90% analyzed by HPLC, and the yield was 51.74% by resorcinol.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 7.5 g of 2,4-DHBA, 60 mL of acetonitrile were sequentially added, 8 mL of concentrated nitric acid was added dropwise, and the temperature was controlled by stirring at 40℃ for 3 hours. After the reaction was completed, the reaction solution was poured into 300 mL of distilled water or 100 g of crushed ice to quench the reaction and precipitate the product, filtered, and the filter cake was dried and ground to obtain a light yellow solid. The mass fraction was 99.79% analyzed by HPLC, and the yield was 49.38% by 2,4-DHBA.

In a 250 mL four-necked flask equipped with a thermometer and a spherical condenser tube, 4 g of 5-nitro-2,4-DHBA, 0.28 g of Pd/C catalyst, 60 mL of ethanol were sequentially added, 7 mL of hydrazine hydrate was added dropwise by using a constant pressure dropping funnel, heated to reflux temperature for 4 h, and the heating was stopped and the reaction solution was filtered while it was hot. The filtrate was placed in an ice water bath and cooled for 30 min. Firstly, 0.1 g of stannous chloride was added, 100 mL of concentrated hydrochloric acid was added, the filtrate was allowed to stand for 6 h, filtered, and the filter cake was dried to obtain an off-white product. The mass fraction of HPLC analysis was 94.83%, and the yield was 66.12% calculated by 5-nitro-2,4-DHBA.