The synthesis of clopidogrel

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Abstract. Cardiac and cerebrovascular disease is a common disease. It is well recognized that antiplatelet agent is effective in the prevention and treatment of thrombosis. Clopidogrel is one of thieno pyridine derivatives, which can inhibit ADP-induced platelet aggregation. The preparation methods of Clopidogrel were reviewed and Clopidogrel was finally synthesized from 2-chlorobenzyl cyanide via bromination, condensation, hydrolyze, esterification, resolution, Finally with the sulfate, re-crystallization product of the target compound clopidogrel. The overall yield is 16%. Synthesis of the intermediate product and finally the structure of the product through ESI and ^{1}H-NMR corroboration. The improved synthetic procedure has the advantage of low cost and is suitable for industrial production.

1. Introduction

Clopidogrel (Clopidogre1), chemical name (S) - alpha - (2 - chlorobenzene base) - 6, 7 - dihydro thiophene and c] [3, 2 - (4 h) pyridine - 5 - methyl acetate and methyl English name (+) - (S) - alpha - chloropheny1 (o) - 6, 7 - dih - ydrothieno [3, 2 - c] pyridine - 5 (4 h) - acetate, is a kind of platelet inhibitors, research by the French Sanofi (Sanofi) company in 1986, with its brand name Plavix (wave d) [1], is a new type of high efficient safety of antiplatelet drugs. A large number of clinical experiments show that it has the advantages of efficacy, safety, and tolerability significantly strong, has the good market prospect. In this paper, synthetic route is as follows:

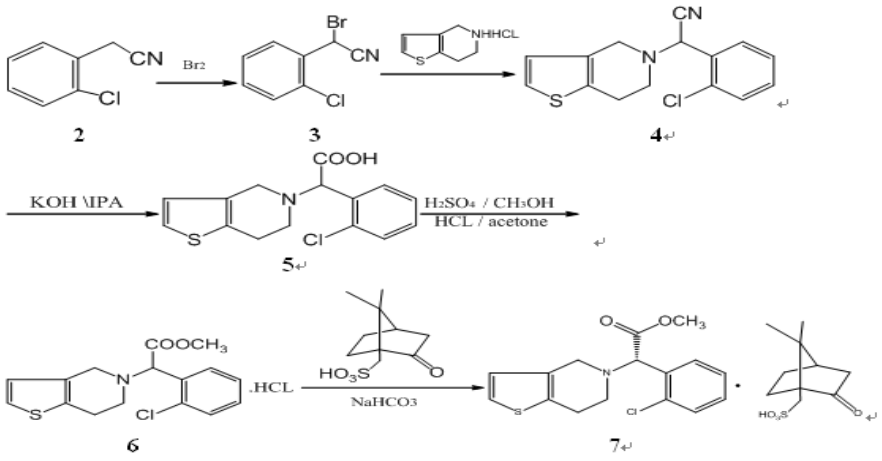

Figure 1. graphics synthetic routes of clopidogrel

2. Experimental Procedures

2.1. Synthetic steps

2.1.1. Join the Chlorobenzyl cyanide in three bottles of apis one after another, three bottles of volume is 500 ml, heated to 100C°, keep the temperature 4 hours, join the methylene chloride 1.0 ml and 1.3 ml water, stirring 10 minutes, let stand for 10 to 15 minutes, to separate the lower organic layer, organic layer add sodium bisulfite 0.6 ml, fully mixing of 15 ~ 20 minutes. Let stand for 10 ~ 15 minutes to separate the organic layer, merged layer, 0.6 ml methylene chloride was used to extract again, merging the organic layer, saturated sodium bicarbonate 0.6 L washing again, with 0.65 L saturated brine washing again, anhydrous magnesium sulfate dry 1 ~ 2 hours, enriching to dry, oily matter, to join the 1.2 ml n-hexane, cooling, stir fully, filter, after fully dry. Light yellow crystal, can be directly into the next step response.

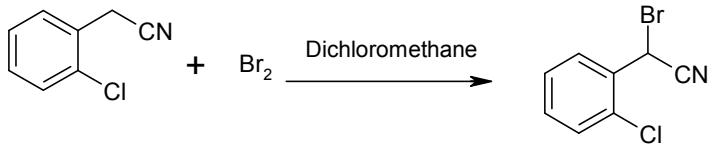

Figure 2. Graphical synthesis of intermediates 3

2.1.2. The results of step1 dissolved in 4.3 ml anhydrous methanol, and then add sodium bicarbonate and pyridine hydrochloride and phase transfer catalyst in turn, after feeding, heating system to reflux, reflux reaction about 5 hours, cooling the system to 0 C°, keep the temperature of mixing 1.5~2 hours, filtration, cake 3 ml water washing 2-3 times, and use 1.4 ml cold methanol washing again, after dry, heating 5 hours, can get white or yellow granular crystalline powder.

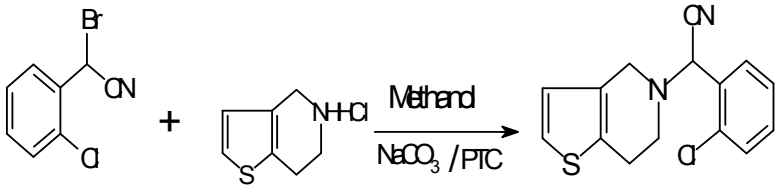

Figure 3. Graphical synthesis of intermediates 4

2.1.3. Potassium hydroxide dissolved in the 3-ml water and cooled to 10 C, then, add clopidogrel , isopropyl alcohol and phase transfer catalyst in turn, heated to reflux while stirring, response more than 8 hours, and then cooled to room temperature, add 6N hydrochloric acid ,PH to 6 ~ 7, system maintain 0 ~ 5 ℃ mixing crystallization of 2 ~ 3 hours, filter, filter cake after fully dry, with 2.5 ml water, cooled to 0 ~ 5 ℃, mixing, filtering, filter cake after dried in a vacuum, 0.08 ~ 0.1 MPa, 40 ~ 45℃ bake for 1 hour, 60℃bake for 8 to 12 hours ,can get white or yellow granular crystal.

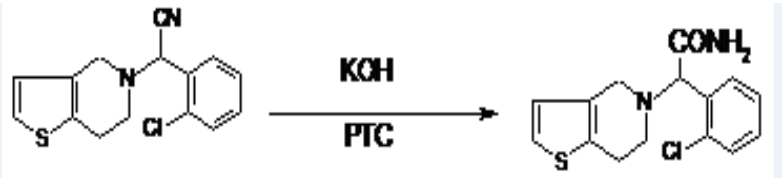

Figure 4. Graphical synthesis of intermediates 5

2.1.4. Clopidogrel acetic acid 1g soluble in methanol, cooling the system to 0℃, then add 1.6 g of sulfuric acid, slow drop, control the temperature in 0 ~ 30℃ when drops, add finished, heating to reflux 24 hours (24 hours can be discrete), after the reaction, cooled to 0 ~ 30℃, Stress concentration to no significant fraction. Cool to 0 ~ 5 ℃, add cold water 4mL slowly , methylene chloride 4 mL, Separation of methylene chloride, use methylene chloride wash the water layerthree times, Combine the methylene chloride layer, add 6 ml water, control the temperature in 0 ~ 5℃, add sodium hydroxide until the solution's PH is 11, continued to stir in low temperature and maintain the PH 11 about 30 minutes, let stand after separated organic layer, water layer use methylene chloride wash twice, combined organic layer, use saturated brine wash again, stress concentration to the dry, get clopidogrel alkali oily matter, to join 5ml acetone in the oily matter, drop hydrochloric acid control temperature 10℃, After the end of droping, Stir for 12 hours, filtering and drying.

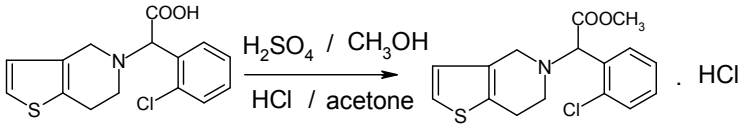

Figure 5. Graphical synthesis of intermediates 6

2.1.5. The results of step4 dissolved in 50 ml anhydrous methanol, partial join sinistral camphor sulfonic acid, stir to dissolve after fully, continue to stir under 25℃ about 2 hours, to join the split clopidogrel camphor sulfonate, keep the temperature of mixing crystallization 48 hours, filter, filter cake with 0.5 L toluene washing, dry, 0.08 ~ 0.10 MPa, drying under 50℃ until 60min then, weighing, add 25ml isopropyl alcohol, heating reflux dissolves, keep back about 0.5 ~ 1 hour, cooled to 0 ℃, mixing 0.5 hours, filter, dry, 0.08 ~ 0.10 MPa, drying under 50℃ until 60min then can get White granular crystal.

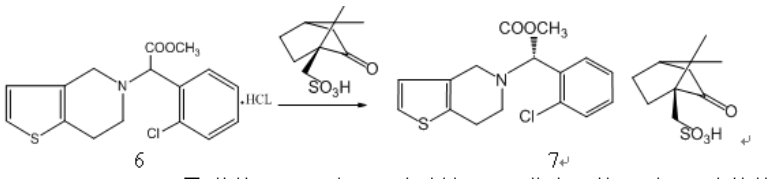

Figure 6. Graphical synthesis of intermediates 7

3. Results and discussion

3.1. The influence of different dosage of catalyst to reaction experiment

In the reaction temperature and reaction time under the condition of invariable, subsequent processing method, fixed amount of other materials besides catalyst, only change (three methyl acetate) the dosage of catalyst, the output of the intermediates, can be observed from the product yield is also different. A total of four experiments, it can be seen when the catalyst is 1.8 g, product yield up to 63.11%.

3.2. The influence of temperature to reaction experiment

Based on reaction rate and the adjustment of the temperature, this experiment adopts bromide and adjacent chlorobenzene acetonitrile ratio of 1.1:1 (mol), reaction temperature of 100℃ for research, find out the most suitable reaction time.ratio of 1.1:1 (mol), reaction temperature of 100℃.

3.3. Different anhydrous ethanol usage influencing on the yield of the product

Holding other conditions unchanged, only in the recrystallization process adding different amount of anhydrous ethanol, observe the product yield, the results available. When add 7.1 g anhydrous ethanol yield up to 12.42.

4. Summary

The preparation methods of Clopidogrel were reviewed and Clopidogrel was finally synthesized from 2-chlorobenzyl cyanide via bromination, condensation, hydrolyze, esterification, resolution, finally with the sulfate, re-crystallization product of the target compound clopidogrel. The overall yield is 16%. Synthesis of the intermediate product and finally the structure of the product through ESI and 1H-NMR corroboration.

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