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Synthesis of pranlukast

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ABSTRACT

4-(4-Phenylbutoxy)benzoic acid **(2)**, which was prepared from tetrahydrofuran **(4)** by ring-opening, Friedel-Crafts alkylation, bromination and etherification, reacted with 3-amino-2-hydroxyacetophenone **(3)** to give 3-[4-(4-phenylbutoxy)benzoic amide]-2- hydroxyacetophenone **(11)**, followed by reacting in the presence of 1H-tetrazol-5-ethyl formate **(12)** and cyclization to give pranlukast **(1)** with the overall yield of 24.7% (based on 4).

KEYWORDS

Pranlukast;
Antagonist;
Synthesis.

INTRODUCTION

Pranlukast **(1)**, with chemical named N-[4-Oxo-2-(1*H*-tetrazol-5-yl)-4H-chromen-8- yl]-4-(4-phenylbutoxy)-benzamide, was developed by Ono Pharmaceutical Co. Ltd. and marketed to Japan in June 1995 for clinic treatment of asthma and anaphylactic rhiniti[1, 2]. Many synthetic methods of 1 had been reported in the literature[3-5] and the researches had focused on the synthesis of two important intermediates 4-(4-phenylbutoxy)-benzoic acid **(2)** and 1-(3-Amino-2-hydroxyphenyl)-ethanone **(3)**. Williamson reaction is a simple way for preparation of intermediate 2 starting from (4-bromo-butyl)-benzene **(7)**, but the synthesis of 7 is so complexity. Hiroaki et al.[6-8] suggested the method of allyl Grignard reagent and oxidion by bromide hydrogen peroxide with 92% yield of 7. Shinzo et al.[9,10] had also reported that 7 could be obtained from γ-butyrolactone undergoing ring-opening, acylating chlorination, Friedel-Crafts reaction, hydrogenation reduction with the yield of 51%. The other method[11, 12] for preparation of 7 also included the substrates of butanedioic anhydride undergoing Friedel-Crafts reaction, reduction and bromation with the yield of 35%. Key intermediate 3 always synthesized from 4-bromophenol. Hirata et al.[13, 14] had reported that 4-bromophenol undergoes Fries rearrangement, nitration, and catalytic hydrogenation to give 3. But most of previous synthetic methods still have some problems, for example, the high cost, the harsh reaction conditions, operational complexity and so on. As a result, it is necessary to develop a plant-scale process which has relatively simple operations, mild reaction conditions, low-cost, and eco-friendly. The great progress in this paper is

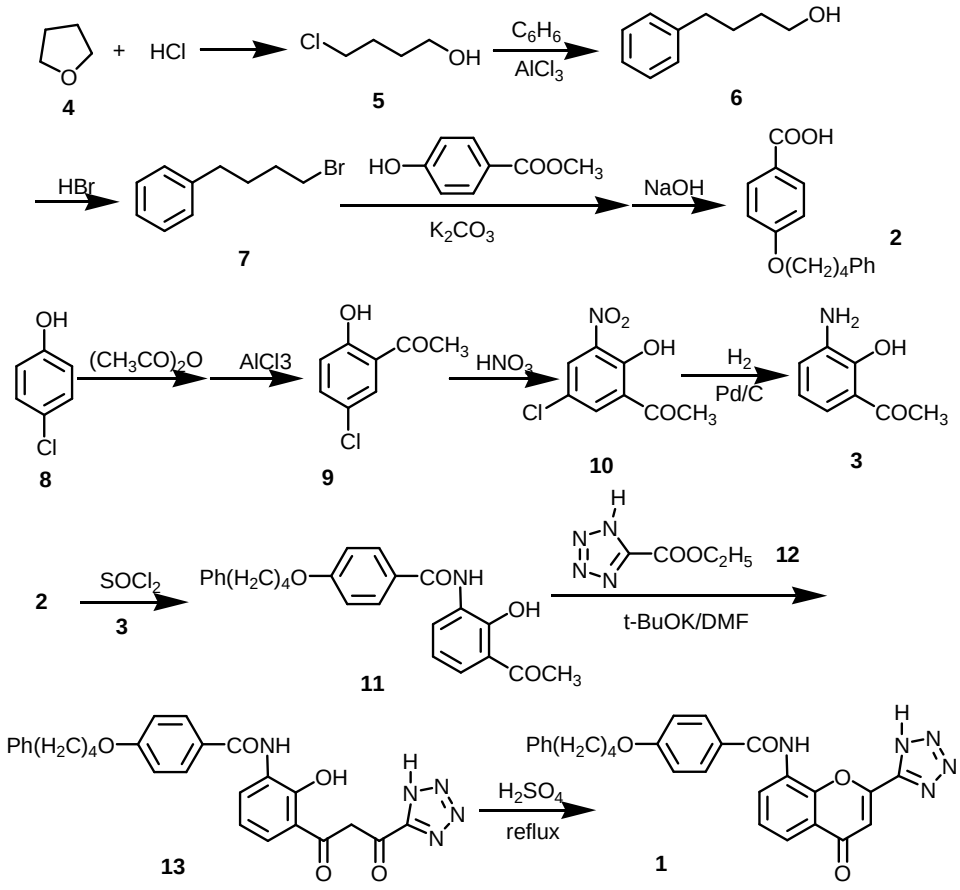
FULL PAPER

aqueous ring-open of tetrahydrofuran **(4)** to give 2 and 4-bromo-phenol was substituted by a much cheaper material 4-chloro-phenol **(8)** for preparation of 3. Furthermore, more detail technologic improvements are also expected.

RESULTS AND DISCUSSIONS

Although it is obvious hydrogen chloride is a good chlorination agent for hydroxygen group[15], but the difficulties of heterogeneous reaction with pressure, equipmental corrosion and emission of excess hydrogen chloride are still problems must be faced to in industrial process. In this study, the ring-opening reaction of 4 under the aqueous reaction was first realized to give 4-chloro-butan-1-ol **(5)** and the usage of hydrochloric acid successfully solved the above problems. Then, 4-phenyl-butan-1-ol **(6)** was obtained from 5 in the presence of aluminum chloride by Friedel-Crafts reactions. In subsequent, 6 was bromined to give 7, and 2 was easily obtained through Williamson reaction with the yield of 41.9% (calculated on the basis of 4). In the preparation of 5, the mole ratio of 4 and hydrochloric acid was 1:3 with the temperature of 60-65°C for 6h and the yield is 70%. Dichloro compound would increase if the temperature or the mole ratio of hydrochloric acid was increased. The hydroxyl group of compound 6 would not alkylate when the mole ratio of 5 and anhydrous aluminium chloride was 1:1.2 with the satisfactory yield of 77.4%. In bromination, 40% hydrobromic acid was used to replace the 60% hydrobromic acid[16] to advoid the corrosion of reactor and the mole ratio of hydrobromic acid to 6 was decreased from 10:1 to 3:1 with the yield of 85%. The technologic key point is toluene was used to bring out water from the system.

The problem of 8 alternating for bromophenol is decrease of activity, especially in hydrogenated elinimating of chloroine. Pd/C catalytic hydrogenation could carry out but need higher temperature (e™50°C) and the Pd/C catalytic activity declined sharply when it was reused for five times and the yield of 3 decreased



Scheme 1 : The synthetic route of 1

to 35.7%. Research also shows that iron and magnesium could only reduce nitro group but not make halogen elemination, zinc could catalyze hydrogenation and elimination but spent more time than bromophenol using as substrate.

EXPERIMENTAL SECTION

All reagents and solvents were commercially available and used without further puriûcation. ^{1}H NMR spectra were obtained from a Varian Spectrospin-AV400 by using TMS as an internal standard. HPLC was performed using Shimadzu LC-10AT systems.

Preparation of 4-chloro-butan-1-ol (compound 5)

Compound **(4)** (144g, 2.0mol) and concentrated hydrochloric acid (600g, 6.0mol) were added to a 1 L three-necked flask. The mixture was warmed to 60-65°C for 6h then cooled down to the ambient temperature and stratified completely. The organic layer was washed with brine to natural, dried with anhydrous magnesium sulfate, filtered and condensed to remove the excess **(4)**. The residue was distilled under vacuum to give the colorless liquid **(5)** (b.p. 62-64°C /50mm Hg, 152g, 70%).

Preparation of 4-Phenyl-butan-1-ol (compound 6)

Anhydrous aluminium chloride (44.3g, 0.33mol) was added to benzene (100mL) below 20°C. The mixture was cooled down to 10-15°C, compound 5 (30g, 0.28mol) was added dropwise in 40min and then maintained for 4h. The reaction mixture was poured into the ice water (100g) containing concentrated hydrochloric acid (10mL) to stratify. The aqueous phase was extracted with benzene (30mL×2) and the collected organic layer was washed with water (100mL×2), dried with anhydrous sodium sulfate, filtrated and concentrated to remove the solvent. The residue was distilled under vacuum to provide colorless liquid **(6)** (b.p. 110-114°C /50mm Hg, 32.1g, 77.4%).

Preparation of (4-bromo-butyl)-benzene (compound 7)

Compound **(6)** (20g, 0.13mol), 40% hydrobromic acid (81g, 0.40mol) and toluene (80mL) were mixed and heated to reflux accompanying with water remove for 2h. The mixture was cooled down to room temperature and the toluene layer was separated. The aqueous phase was extracted with dichloromethane (50mL×2). The combined organic phase was dried with anhydrous sodium sulfate, filtrated, concentrated and distilled under vacuum to obtain compound **(7)** (b.p. 98-102°C /50mm Hg, 23.8g, 85%).

Preparation of 4-(4-phenyl-butoxy)-benzoic acid (compound 2)

Compound **(7)** (15g, 0.07mol), DMF (15mL), toluene (45mL), methyl 4-hydroxybenzoate (11.5g, 0.076mol) and anhydrous potassium carbonate (15.4g, 0.11mol) were mixed and warmed to reflux for 10h. 15% Aqueous sodium hydroxide (100mL) was added into the mixture. The mixture was refluxed for 1h and then cooled down to room temperature. 10% Hydrochloric acid (200mL) was added to the mixture to adjust pH 2. The white solid **(2)** (18.8g, 92%) would be obtained after filtering, washing with water(100mL) and drying. ^{1}H NMR(TMS) δppm: 1.82-1.85(m, 4H, methylene), 2.70(t, 2H, methylene), 4.04(t, 2H, methylene), 6.91(d, *J*=8.0Hz, 2H, phenyl), 7.11-7.26(m, 3H, phenyl), 7.28(t, 2H, phenyl), 8.04(d, *J*=8.4Hz, 2H, phenyl).

Preparation of 1-(5-chloro-2-hydroxy-phenyl)-ethanone (compound 9)

Compound **(8)** (156.6g, 1.00mol), acetic anhydride(121g, 1.18mol) and pyridine(22mL) was mixed and heated to reflux for 3h. Then the mixture was evaporated under vacuum to remove pyridine, acetic acid and the excess acetic anhydride. The residue was added dropwise into a mixture of aluminum chloride (253.5g, 1.90mol) and tetrachloroethylene (430mL) and heated to reflux for 1.5h. The mixture was cooled down to 100°C and then poured into 5% hydrochloric acid (1.35L), extracted with dichloromethane (150mL ×2) and decolorized with activated charcoal. The gray crystal compound **(9)** (157g, 79%) was obtained when the solvent was removed under vacuum. M.p. 58.5°C(from dichloromethane). ^{1}H NMR(TMS) δppm: 12.12(s, 1H, hydroxy), 7.67(s, 1H, phenyl), 7.40-7.37(d, J=11.2Hz, 1H, phenyl), 6.95-6.93 (d, J=8.8Hz 1H, phenyl), 2.62(s, 3H, methyl).

Preparation of 1-(5-chloro-2-hydroxy-3-nitro-phe-

FULL PAPER

nyl)-ethanone (compound 10)

Compound **(9)** (37.7g, 0.19mol), tetrachoromethane (120mL) and 65% nitric acid (26.3gў0.27mol) were mixed and heated to reflux for 20min. Then the mixture was cooled down to 0°C. The suspension was filtrated and the filter cake was washed with water (200mL) and dried to provide yellow solid compound **(10)** (41.2g, 90%). M.p. 102.5°C(from tetrachoromethane).

Preparation of 1-(3-Amino-2-hydroxy-phenyl)-ethanone (compound 3)

Compound **(10)** (39.0g, 0.16mol), 5% Pd/C (8.4g, 0.007mol), dichloromethane (300mL), methanol (320mL), concentrated hydrochloric acid (20mL) and water (80mL) were added into a hydrogenation flask. Make the flask vacuum and replace of air by nitrogen and hydrogen for three times in proper order. Hydrogenation was carried out under the ambient pressure until the absorption of hydrogen stop (20h). The mixture was filtered and concentrated under vacuum to remove the solvent. After decolorization by the activated charcoal, the mixture was filtrated and saturated sodium bicarbonate was added to the filtrate to adjust pH 7. The suspension was filtrated to provide ginger solid **(3)** (18.0g, 70%). M.p. 96°C(from water). ^{1}H NMR(TMS) δppm: 12.47(s, 1H, hydroxy), 7.15(d, *J*=8.0Hz,1H, phenyl), 6.88(d, *J*=7.2Hz,1H, phenyl), 6.73(t, 1H, phenyl), 3.91(s, 2H, amino), 2.64(s, 3H, methyl).

Preparation of N-(3-Acetyl-2-hydroxy-phenyl)-4-(4-phenyl-butoxy)-benzamide (compound 11)

Compound **(2)** (13.5g, 0.05mol), toluene (50mL), DMF (0.125mL) and sulfoxide chloride (6.60g, 0.05mol) were mixed and heated to 60-75°C for 0.5h. The mixture was cooled down to the room temperature. The obtained acyl chloride was reserved and standby for use.

The above prepared acyl chloride and 8.48% sodium carbonate aqueous solution were added dropwise at the same time to a solution of compound 3 (7.53g, 0.05mol) and toluene (100mL) at 40-45 °C within 1 h. The mixture was kept at 40-45°C for 2h. Then 10% hydrochloric acid (250mL) was added to the mixture to adjust pH 7. After the extraction by toluene, the organic phase was combined, washed with water (100mL×3), dried with anhydrous sodium sulfate, filtrated and evaporated to dry to provide faint yellow crystal compound 11 (17.1g, 85%). ^{1}H NMR(TMS) δppm: 1.83-1.86(m, 2H, methylene), 2.67(s, 3H, metyly), 2.71(t, 2H, methylene), 4.04(t, 2H, methylene), 6.954-6.976(d, *J*=8.8Hz, 2H, phenyl), 7.21(t, 3H, phenyl), 7.28(t, 1H, phenyl), 7.48(d, *J*=9.2Hz, 1H, phenyl), 7.87(d, *J*=8.8Hz, 2H, phenyl), 8.58(s, 1H, amide), 12.98(s, 1H, hydroxy).

Preparation of N-{2-Hydroxy-3-[3-oxo-3-(1H-tetrazol-5-yl)-propionyl]-phenyl}- 4-(4-phenyl-butoxy)-benzamide (compound 13)

Compound **(11)** (12.1g, 0.03mol) and 12 (5.2g, 0.04mol) were added to a solution of potassium *tert*-butoxide (23.5g, 0.21mol) and DMF (150mL) with continuous stir under a nitrogen atmosphere. The mixture was warmed to 45 °C for 4h then cooled down to room temperature and poured into 5% hydrochloric acid (500mL). The mixture was filtrated and the filter cake was washed with water (160mL) to neutral and dried. After recrystallization with ethyl acetate the faint yellow solid compound **(13)** was obtained (12.2g, 81.5%). ^{1}H NMR(TMS) δppm: 1.74-1.77(m, 4H, methylene), 2.48(t, 2H, methylene), 3.34(s, 2H, methylene), 4.10(t, 2H, methylene), 6.89(s, 1H, benzopytan), 7.084-7.114(d, *J*=12.0Hz, 2H, phenyl), 7.17-7.29(m, 5H, phenyl), 7.49 (t, 1H, phenyl), 7.88 (d, *J*=12.4Hz, 1H, phenyl), 8.05 (d, *J*=14Hz, 2H, phenyl), 8.10 (d, *J*=2.0Hz, 1H, phenyl), 10.0(s, 1H, hydroxy).

Preparation of pranlukast (compound 1)

Compound **(13)** (5g, 0.01mol), methanol (50mL) and sulfuric acid (0.5ml) were mixed with stirring and heated to reflux for 3h. After cooled down to room temperature, water (20mL) was added into the mixture and the mixture was kept at -10°C for 4h. The faint yellow solid was obtained after filtration. Then it was recrystallized with toluene to obtain white solid compound **(1)** (4.1g, 85.1%). M.p. 243°C(from toluene). Content 99.1% (HPLC). ^{1}H NMR(TMS) δppm: 1.72-1.75(m, 4H, methylene), 2.48(t, 2H, methylene), 4.08(t, 2H, methylene), 7.07(d, *J*=12.0Hz, 2H, phenyl), 7.15~7.28(m, 3H, phenyl), 7.58(t, 1H, phenyl), 7.60(d, *J*=2.4Hz, 1H, phenyl), 7.90(d, *J*=10.8Hz, 2H, phe-

nyl), 8.30(d, *J*=6.0Hz, 1H, phenyl), 8.78(s, 1H, benzopytan), 9.38(s, 1H, amide).

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