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Research Article

Multi-step synthesis of pharmaceutical impurities of Citalopram by modifying the reaction medium to increase reaction yields

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ABSTRACT

Citalopram's popularity comes from its treatment in depression; however pharmacologists are starting to find further uses for this drug. Depression is often linked with anxiety disorders; their symptoms in many cases are interchangeable. Citalopram is often used if the patient is suffering from depression, but they suddenly get panic symptoms. Citalopram is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI).In pharmaceutical companies when the citalopram was synthesized same impurity are produced as byproducts. Today, identification of this compound was performed by using pharmacopeia standards. For this aim, this article relates to processes for the preparation of 5-Bromophthalide of Formula (5), important use of this compound as an impurity for the citalopram drug.

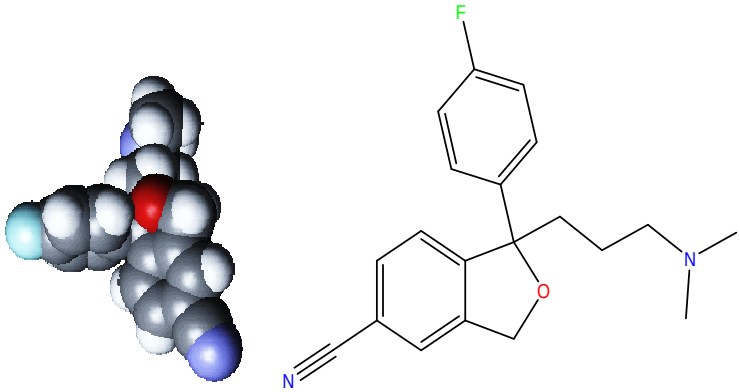


Fig. 1. The structure of citalopram

Keywords: Citalopram, Pharmacopeia impurity, Phtalimide, Hydrogenation reaction.

Research Highlights

- Syntheses of HPLC standards of citalopram drug.
- Using Raney Ni catalyst instead of Pd/C catalyst for hydrogenation reaction

INTRODUCTION

Citalopram was first synthesized in 1972 by scientists at the pharmaceutical company Lundbeck [1,6]. Citalopram is so interesting compound duo to its applications for treatment

in depression; however pharmacologists are starting to find further uses for this drug. Depression is often linked with anxiety disorders; their symptoms in many cases are interchangeable. Citalopram is often used if the patient is suffering from depression, but they suddenly get panic symptoms. The drug has also been seen to improve the quality of life of patients with panic disorder [2].

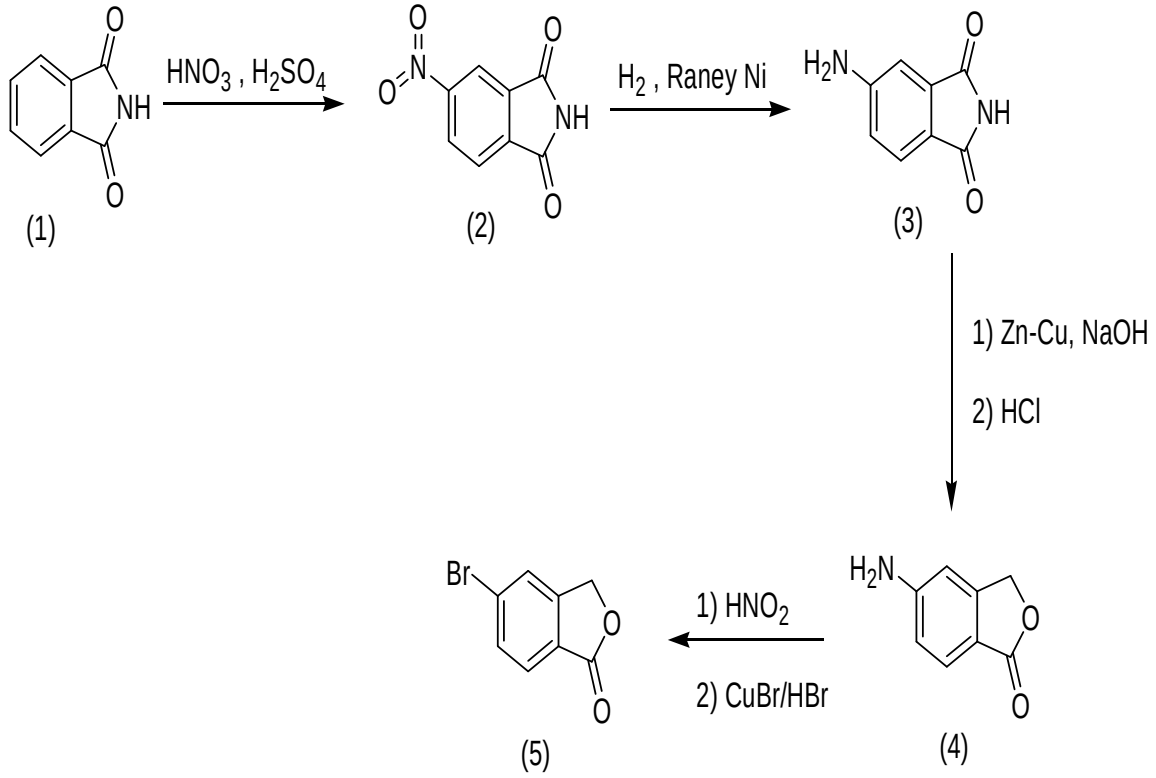
Recent studies have shown the drug gives a positive response in the treatment of binge eating disorder [3]. The drug also has potential in the treatment of other eating disorders such as bulimia. Due to these findings scientists are researching the role of citalopram in the treatment of anorexia [4]. Initial findings have been quite encouraging [5].

Every medicines have individual impurities. These impurities were produced during synthesis of medicine. The formation of these impurities in the drug synthesis process is unavoidable. Thus, quality control of produced medicines presence and amount of the impurities is very important. For this purpose, this article relates to processes for the preparation of 5-Bromophthalide of Formula (5), important use of this compound as an impurity for the citalopram drug. The advantage of the presented method in this paper is the high yield and also collecting a comprehensive method for industrial production of these impurities. This method performed based on reduce overall costs of final production.

MATERIALS and Methods

All used materials were purchased from Sigma Aldrich and melting point analysis was taken by BUCHI Melting Point B-545.

Experimental

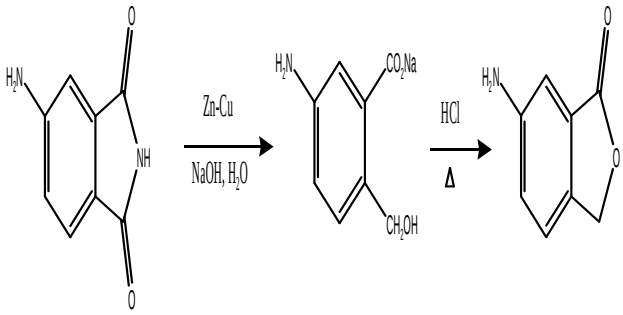


Synthesis of 4-nitrophtalimide (2):The mixture of nitric acid (0.27 mol) and sulfuric acid (1.62 mol) was stirred in an ice bath maintained for 30 min to room temperature.

The phtalimide (1) was added dropwise to acidic solution and heated at 35 ºC while stirring until a colorless solution was achieved. After stirring for 4 h, the white solid was precipitated from ice water, filtered and washed with water. The resultant Crude was dried under ambient conditions. 83% yield; Melting point : 196-202°C.[7]

Synthesis of 4-aminophthalimide (3):4-Nitrophthalimide (2) (100g, 0.52mol) was taken into a hydrogenation vessel and dissolved using 600ml of dimethyl formamide. Raney nickel catalyst (20gr, wet) was added to the solution and hydrogenated initially at 20-30°C under 20-40psi pressure. After the exothermic nature of the reaction was over, hydrogen pressure was increased to 40-60psi and the temperature to 40-50°C. After the hydrogenation is over the reaction mixture was filtered while hot and the catalyst removed by filtration. Dimethylformamide was removed from 10 the filtrate under reduced pressure at 60-80°C. Water (500ml) was added to the residue and the mixture stirred for 20-30 min. The product was isolated by filtration and dried at 60-70°C to get a yellow crystalline solid of 4-aminophthalimide**.** 97% yield. Melting point: 293-5°C.[8]

Synthesis of 5-aminophthalide (4):180 g (2.75 gram atoms) of zinc dust is stirred to a thick paste with a solution of 1 g of copper sulfate in 35 ml of water, and (327 ml) of 20 percent aqueous sodium hydroxide is added. The contents arecooled to 5° by means of an ice bath, and 4-aminophthalimide (3) (162 g, 1 mol) is added in small portions. Stirring is continued for 2h.The mixture is diluted with 400 ml of water, warmed on a steam bath until evolution of ammonia has ceased 3h, and concentrated to a volume of about 400 ml by distillation under reduced pressure. The material is filtered and the filtrate made acid with concentrated hydrochloric acid. The mixture is boiled for1h in order to complete the lactonization of the hydroxymethylbenzoic acid. The crude 5-aminophthalide, is recrystallized from water. 70%yield
Melting point : 177-189 °C [9].



Synthesis of 5-Bromophthalide (5):A mixture of 5-aminophthalide(4) (16.8 g, 0.11mol)in (34 ml) 48% aqueous hydrobromic acid was cooled to 0° in an ice bath and a solution of 7.8 gm sodium nitrite in 15 ml water was added at less than 5°, using internal ice cooling as necessary. The nitrosation mixture was stirred for an additional 30 minutes at about 0° with an excess of nitrous acid. After 30 minutes, the diazonium salt was added portion wise over about 35 minutes to a mixture of 28.2 g freshly prepared cuprous bromide and 18 ml 48% aqueous hydrobromic acid at room temperature (the bulk of the diazonium salt was maintained at about 0°). The temperature of the reaction mixture rose to about 38° and considerable frothing occurred. The mixture was stirred for 1h, and then the product was filtered off and washed neutral with water. Recrystallization from 100 ml isopropanol.66% Yield. White to Pale Yellow Crystalline Solid with melting point: 153 -162 °C. [10]

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