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Green and Efficient Synthesis of Baclofen

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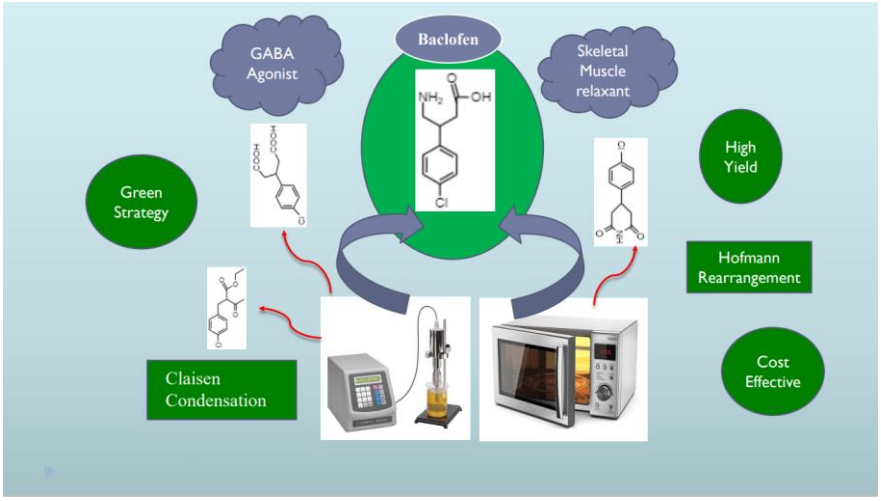
ABSTRACT

Baclofen is a Gamma Amino Butyric acid (GABA) agonist to relax skeletal muscles. It is especially effective in treating muscular spasticity. In this research, we now describe the synthesis of Baclofen using a new approach which begins with 4- chlorobenzaldehyde. We have carried all reactions by the green method. It gives the better yield. The identity of this product was confirmed by spectral analysis and compared with the standard Baclofen. New and eco-friendly approach was developed for the synthesis

GRAPHICAL ABSTRACT



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1. Introduction

Baclofen is a gamma amino butyric acid (GABA) agonist for skeletal muscle relaxation. It is especially effective in treating spasticity. It interacts with both GABAA and GABAB receptors [1-3]. Mostly the GABA-A receptors are primarily found in the frontal lobe, GABA B receptors are more commonly found in the thalamusand the dorsal horn of the body's spinal cord [3-5]. Very fast synaptic suspension is mediated by GABAA receptors linked to chloride ion channels in the cells. GABA-B receptors are insensible to bicuculline and linked to neuronal potassium and different calcium channels through G-proteins, allowing them to mediate delayed synaptic inhibition by raising potassium and lowering calcium conductance [6-7]. The antispasmodic and muscle relaxant baclofen, which is presently the sole selective and therapeutically relevant GABAB agonist, activates the GABAB receptors [8]. There are various accounts in the literature concerning the synthesis of Baclofen because of its biological and pharmacological value [9]. Although these publications employ diverse methodologies, the reagents used are costly [10-11], or the yield is poor. There are different methods used in the synthesis [12-18]. Various methods are used during the synthesis, including the preparation of various nanoparticles from plant materials [18-24]. In most cases, plant-derived nanoparticles are synthesizedusing phytochemical analysis [25-32]. A variety of heterocyclic compounds are synthesized using the Green Approach [33-35]. An alternate strategy to the synthesis of Baclofen is discussed in this work, which produces a high-yielding product and green pathway used for the synthesis. We have carried out the experiments by using green protocol, various new catalyst is used for reaction. We have reduced the cost of the production. All reaction gives above 80 % yield.

2. Experimental

All chemical components were reagent grade and analyzed using TLC on silica gel plates and U.V. light. Shimadzu IR 120 without KBR pellet was used to record I.R. spectra. Varian-400 spectrometer was used to record 1HNMR spectra.

2.1. Procedure for the synthesis of pchlorobenzylidene-bis-acetoacetic ester (Step I)

A mixture of 2.8 gm of the para -chlorobenzaldehyde and 5.2 g of ethyl acetoacetate was treated at 0 °C with 4 mL of Morphiline as a base, kept it at 0-5 °C for 60-70 min. Then, it was sonicated at 20-25 °C for 12 hours. After that, 20.0 ml of ethanol was added slowly. The reaction mixture was completely cooled and filtered. The residue was washed with 70% ethanol until a solid white product was obtained.

2.2. Synthesis of β(chlorophenyl) glutaric acid derivative (Step II)

The solution was taken to have a temperature of 50-60 ^{0}C of 20.0 g of Lithium hydroxide in 15.0 mL water added to para -chlorobenzylidene-bisacetoacetic ester, which was prepared in step I. Then, this reaction mixture was subjected to sonication during this maintenance at 90-95 °C for almost 1 hour. After that, check the reaction progress using thin layer chromatography. After completing the reaction, the reaction mixture was diluted with two volumes of water. Wash the aqueous layer washed with ether. Then acidify the aqueous layer with 5.5 mL of concentrated hydrochloric acid and chilled thoroughly and filtered. The filter cake was washed several times with ice water and dried in the vacuum on a rot evaporator at 60 °C, then dry it properly.

2.3. Synthesis of β(pchlorophenyl) glutarimid (Step III)

1.5 g. of β(p-chlorophenyl) glutaric acid was taken and synthesized in step II. Then, it was dissolved in 10.0 mL of distilled water. Next, 3.5 mL of concentrated ammonium hydroxide was added to this reaction mixture. After that, the color of the solution was removed. The solution was treated with charcoal and filtered over the hyflo. Then, the mixture was heated in a proper open flask until the mixture microwave oven reached product formation and checked using the thin layer chromatography. Then after, 5 ml of the alcohol was added. The resulting reaction mixture was heated in the microwave until boiling. The completion was then diluted with 100 ml of hot water, stirred, completely cooled, and filtered. Finally, the filter cake was rinsed with ice water and dried in vacuum at 60 °C.

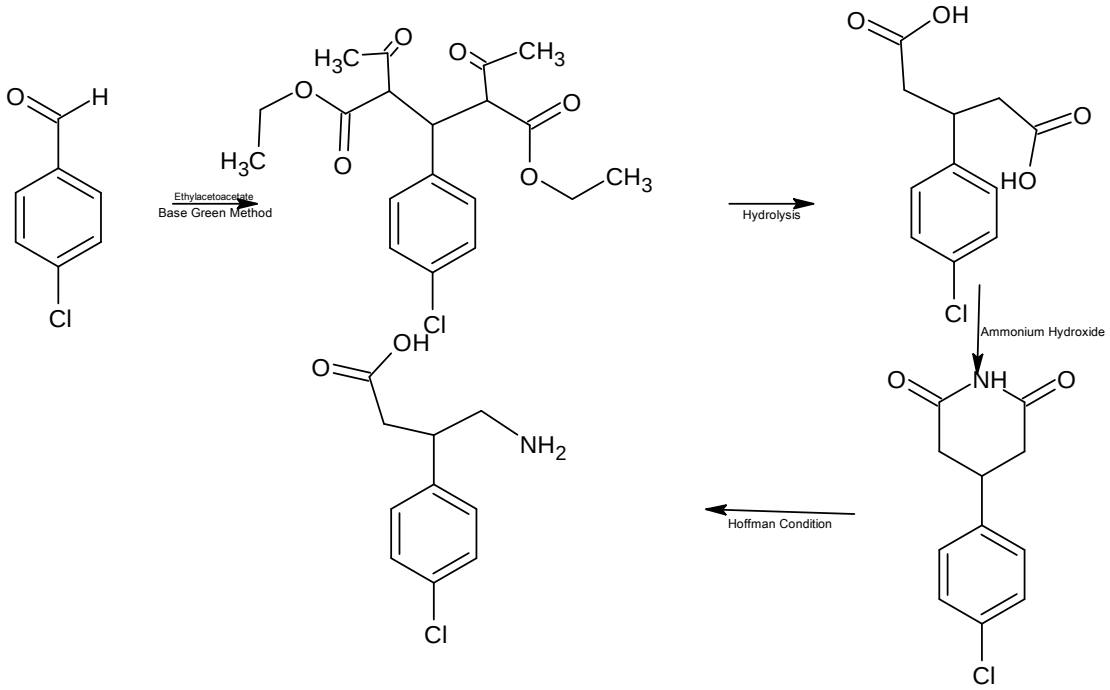

Fig. 1 Process for synthesis for balcofen

2.4. Procedure for the synthesis of 4-Amino-3-(4-chlorophenyl) butanoic acid (Baclofen) (Step IV)

0.5 g of the above product β (p-chlorophenyl) glutarimide was cooled to 10 °C to 15 °C in anice bath. Next,to this reaction mixture, a solution of0.5 g of sodium hydroxide in 2.0 mL of water was prepared, and then0.4 g of bromine was added to the above reaction mixture over 20 minutes. The reaction mixture was thensonicated at 20-25 °C. for 4 hours. The reaction solution was then carefully adjusted to pH=7 with dilute hydrochloric acid (this is an important step). The microcrystalline 4-amino 3 (4-chlorophenyl) fatty acid (γ-amino β (p-chlorophenyl) fatty acid) is then separated asa product. The product was washed witha suitable solvent.

3.Result and Observations

3.1.P-chlorobenzylidene-bis-acetoacetic ester

Yield:91%;

MP: 153-156 °C;

IR (Without KBr); υ 654, 828, 1470, 1580, 1720, 1740, 2960,3180, 3560, cm^{-1};

1HNMR (400 MHz, CDC13): δ 1.2 (2t, 6H), 1.5 (s, 3H), 2.9 (m,3H), 3.8 (m, 4H), 7.28 (q, 4H).

3.2.Synthesis of β(pchlorophenyl) glutaric acid

Yield:90%;
MP: 165-169°C;
IR (without KBr); υ 648, 828, 968, 1498, 1590, 1715, 2480-3420, cm^{-1};
1HNMR (400 MHz, CDC13): δ2.7 (m, 4H), 3.4 (m, 1H), 7.5 (m, 4H), 12 (s, 2H).

3.3. β(p-chlorophenyl) glutarimid

Yield:88%;
MP: 128-129°C;
IR (without KBr); υ 640, 820, 960, 1490, 1600, 1710, 2400-3400, cm^{-1};
1HNMR (400 MHz, CDC13): δ2.7 (m, 4H), 3.4 (m, 1H), 7.5 (m, 4H), 12 (s,2H).

3.4. 4-Amino-3-(4-chlorophenyl) butanoic acid (baclofen)

Yield:88%;
MP: 208-209°C;
IR (without KBr); 1098, 1498, 968, 1538, 1610, 1585, cm^{-1}.

4. Results and Discussion

We performed all the reactions on the Greenway. Various condensation reactions were used such as B. Claisen condensation. It is condensed to form a cyclic imide, and finally forms a Hofmann rearrangement. All three reactions can follow the general procedure used for the Green Protocol. In the reaction of ethyl acetoacetate with chlorobenzaldehyde, it is used in the alkoxide sodium / reaction to make ethyl acetoacetate an active nucleophile or to form a nucleophile that excels in the reaction required for Claisen condensation. Strong bases such as other bases are required. The primary medium can be further used for hydrolyzing ester molecules very easily to form acid molecules. Finally, the reaction of (Pchlorophenyl) glutaric acid with ammonium hydroxide or other bases can be used to produce (Pchlorophenyl) glutarimide. Next, in the Hofmann rearrangement, the reaction between bromine and sodium hydroxide is converted into an imide, carbon dioxide is removed after hydrolysis, and baclofen is used as the final API.

5. Conclusion

To sum up, the synthesis of the different baclofen derivatives is in the final step. This study proposes a 4-step green, the cost-effective, straightforward, and synthetic pathway that has the potential for large-scale drug creation in the industrial synthesis of the product. This green strategy is used for Baclofen synthesis. During this, the synthetic approach uses inexpensive chemicals and leads to an overall yield of around 80% along with different green protocols.

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