ICC
Iranian Chemical Communication
Original Research Article
Payame Noor University http://icc.journals.pnu.ac.ir

A facile and efficient synthesis of Baclofen

Ali Saberi

Chemistry Department, Payame Noor University, 19395-4697 Tehran, Iran

Received: 30 March 2015, Accepted: 4 October 2015, Published: 1 April 2016

Abstract

γ-Aminobutiric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, is activated by the antispastic and muscle relaxant agent, Baclofen, which is a lipophilic derivative of GABA. Since 1962 several strategies have been reported for the synthesis of baclofen. In this study, baclofen was easily synthesized by Claisen condensation of ethyl acetoacetate and *p*-chlorobenzaldehyde, which is formation of cyclic imide from β(*p*-chlorophenyl) glutaric acid and further Hoffmann rearrangement of β(*p*-chlorophenyl) glutarimid with a good yield.

Keywords: Baclofen; synthesis; GABA receptor; γ-aminobutiric acid.

Introduction

γ-Aminobutiric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. It interacts with two types of receptors, GABAA and GABAB [1]. GABAA receptors are mainly in the frontal cortex, but GABAB receptors predominate in the thalamus and the dorsal horns of the spinal cord [2]. GABAA receptors are coupled with chloride ion channels and mediate fast synaptic inhibition. GABAB receptors are insensitive to bicuculline which are coupled through G-proteins to neuronal potassium and calcium channels and mediate slow synaptic inhibition by increasing potassium and decreasing calcium conductances [3]. GABAB receptors are activated by the antispastic and muscle relaxant agent, baclofen, which is the only selective and therapeutically useful GABAB

*Corresponding author: Ali Saberi
Tel: +98 (912) 3933625, Fax: +98 (21) 76400890
E-mail: saberi@pnu.ac.ir, saberi121@gmail.com

agonist currently used [4]. Because of its biological and pharmacological importance, there are several reports in the literature about the synthesis of baclofen. Although different strategies have been applied in these reports, the reagents used are expensive or the yield is low [5-8]. In this paper, an alternative approach to the synthesis of baclofen is described which gives the product with a good yield (Figure 1).

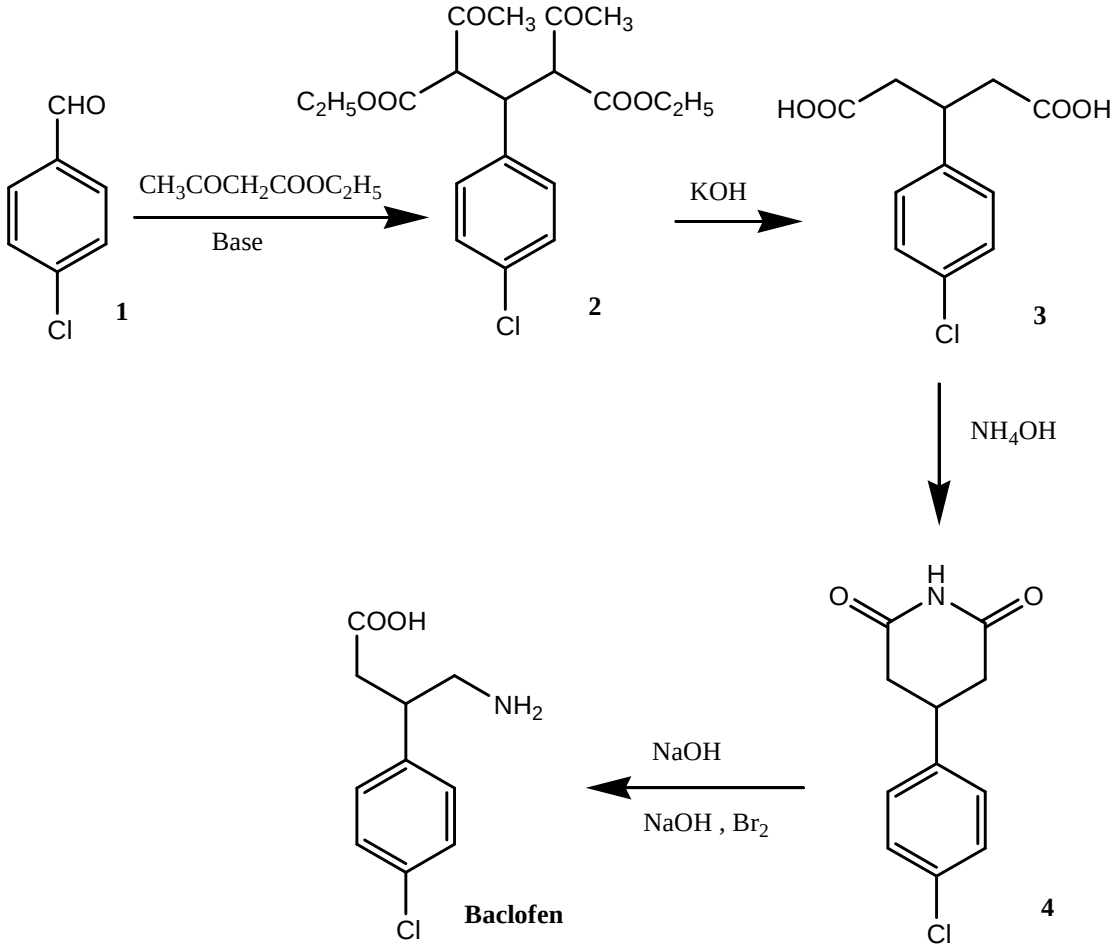

Figure 1.

Experimental

General

All the chemical compounds were from the Merck Company and of analytical grades. Thin layer chromatography (TLC) was performed on pre-coated silica gel plates (E Merck, Silica gel 60F254, 0.25mm). IR Spectra were recorded on Perkin-Elmer model 840. ^{1}HNMR spectra were recorded on varian-400 spectrometer.

Procedure for the synthesis of p-chlorobenzylidene-bis-acetoacetic ester (2)

A mixture of 28 g of *p*-chlorobenzaldehyde and 52 g ethyl acetoacetate was treated at 0°C with 4 mL of piperidine, allowed to stand at 0-5 °C for one hour and stirred at 20-

25 °C for 24 hours. Then, 200 mL absolute ethanol was added. The reaction mixture was thoroughly chilled and filtered. The precipitate was washed with a 50% ethanol until white product appears.

P-chlorobenzylidene-bis-acetoacetic ester (2)

Yield:85%; mp: 153-156 °C; IR (KBr); υ 650, 825, 1465, 1600, 1715, 1735, 2980, 3100, 3520, cm^{-1}; ^{1}HNMR (400 MHz, $CDC1_3$): δ 1 (2t, 6H), 1.3 (s, 3H), 2.7 (m, 3H), 3.9 (m, 4H), 7.22 (q, 4H).

Procedure for the synthesis of β(p-chlorophenyl) glutaric acid (3)

A stirred hot solution of 200 g of potassium hydroxide in 150 mL of water was added portionwise to p-chlorobenzylidene-bis-acetoacetic ester. The reaction mixture was stirred and maintained at 90-95 °C for 2 hours, diluted with two volumes of water, washed with ether, acidified slowly with 550 mL of concentrated hydrochloric acid, chilled thoroughly and filtered. The filter cake was washed several times with ice water and dried in vacuo at 60 °C.

β(p-chlorophenyl) glutaric acid (3)

Yield:88%; mp: 166-168°C; IR (KBr); υ 640, 820, 960, 1490, 1600, 1710, 2400 - 3400, cm^{-1}; ^{1}HNMR (400 MHz, $CDC1_3$): δ 2.6 (m, 4H), 3.3 (m, 1H), 7.4 (m, 4H), 12 (s, 2H).

Procedure for the synthesis of β(p-chlorophenyl) glutarimid (4)

15 g of β(p-chlorophenyl) glutaric acid was dissolved in 100 mL of water and 35 mL of concentrated ammonium hydroxide. The solution was charcoaled and filtered and then heated in an open flask until the temperature of the mixture reaches 200 °C. The temperature was maintained for 30 minutes and then cautiously diluted with 50 mL of absolute ethanol, heated to boiling, diluted with 100 mL of hot water, stirred, cooled thoroughly and filtered. The filter cake is washed with ice water and dried in vacuo at 60 °C.

β(p-chlorophenyl) glutarimid (4)

Yield:78%; mp: 125-129°C; IR (KBr); υ 640, 820, 960, 1490, 1600, 1710, 2400 - 3400, cm^{-1}; ^{1}HNMR (400 MHz, $CDC1_3$): δ 2.6 (m, 4H), 3.3 (m, 1H), 7.4 (m, 4H), 12 (s, 2H).

Procedure for the synthesis of 4-Amino-3-(4-chlorophenyl) butanoic acid (baclofen)

5 g of β(p-chlorophenyl) glutarimid is cooled to 10° to 15 °C. At this temperature, a solution of 5 g of sodium hydroxide in 20 mL of water and then, in the course of 20 minutes, 4 g of bromine were added. When all has been dropped in, the batch was stirred for 8 hours at 20° to 25 °C. The reaction solution was then cautiously adjusted with

concentrated hydrochloric acid to pH=7, whereupon finely crystalline 4-Amino-3-(4-chlorophenyl) butanoic acid (γ-amino-β-(p-chlorophenyl) butyric acid) settles out. To purify, it was recrystallized from water.

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

Yield:81%; mp: 206-208°C; IR (KBr); υ 1095, 1495, 960, 1530, 1600, 1575, cm^{-1}.

Results and discussion

This strategy includes three general steps; 1) Claisen condensation, 2) formation of cyclic imide, 3) Hoffmann rearrangement.

The reaction of ethyl acetoacetate and *p*-chlorobenzaldehyde needs a strong base such as sodium alkoxide to make the ethyl acetoacetate an active nucleophile which, in turn, undergoes a Claisen condensation too. Hydrolysis of the ester compound may also be performed in a basic medium. For the preparation of β (*p*-chlorophenyl) glutarimid, β (*p*-chlorophenyl) glutaric acid needs to react with ammonium hydroxide. According to Hofmann rearrangement, the reaction of bromine with sodium hydroxide transforms imide to give off carbon dioxide and baclofen obtained.

Conclusion

As a conclusion, this paper presents a 4-step facile and economic synthetic route provided a potential for the large-scale preparation of the drug in the industrial setting and the strategy could be exploited for the preparation of baclofen. The synthetic method involves cheap reagents and gives the product with about 50% overall yield.

Acknowledgments

The author is grateful to Payame Noor University for financial support.

References

[1] D.R. Hill, N.G. Bowery, *Nature (London)*, **1981**, *290*, 149-152.

[2] N.G. Bowery, A.L. Hudson, G.W. Price, *Neuroscience (Oxford)*, **1987**, *20*, 365-368.

[3] N.G. Bowery and G.D. Pratt, *Arzneim Forsch/Drug Res*, **1992**, *42*, 215-223.

[4] D. A. Williams and T. L. Lemke, *Foye's Principles of Medicinal Chemistry, 5th Ed. Lippincott Williams & Wilings, Philadelphia*, **2002**, 492-503.

[5] T. Ibuka, A. Schoenfelder, P. Bildstein and A. Mann, *Synth. Commun.*, **1995**, *25*, 1777-1782.

[6] F. Coelho, M. B. M. De Azevedo, R. Boschiero and P. A. Resende, *Synth. Commun.* , **1997**, *27*, 2455-2465.

[7] R. Chenevert and M. Desjardins, *Tetrahedron Lett.*, **1991**, *32*, 4249-4250.

[8] N. Longlois, N. Dahuron and H. S. Wang, *Tetrahedron*, **1996**, *52*, 15117-15126.