Original Article

Synthesis of Baclofen; an Alternative Approach

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Abstract

γ-Aminobutiric acid (GABA), the major inhibitory neurotransmitter in the central nervous system has two major receptor subtypes ($GABA_A$ and $GABA_B$). $GABA_B$ receptors are 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 an approach has been made to synthesize baclofen in an alternative way. The key steps involved the condensation of p-chloro benzaldehyde with nitromethane and the reaction of β-nitro styrene thus prepared with malonate diethyl ester. Further reduction and decarboxylation of the product gave access to baclofen with a good yield.

Keywords: Baclofen; Synthesis; GABA receptor; Agonist.

Introduction

γ-Aminobutiric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. It interacts with two types of receptors, $GABA_A$ and $GABA_B$ (1). $GABA_A$ receptors are mainly in the frontal cortex but $GABA_B$ receptors predominate in the thalamus and the dorsal horns of the spinal cord (2). $GABA_A$ receptors are coupled to chloride ion channels and mediate fast synaptic inhibition. $GABA_B$ receptors are insensitive to bicuculline are coupled through G-proteins to neuronal potassium and calcium channels and mediate slow synaptic inhibition by increasing potassium and decreasing calcium conductances (3). $GABA_B$ receptors are activated by the antispastic and muscle relaxant agent, baclofen, which is the only selective and therapeutically useful $GABA_B$ agonist currently used (4). Because of its biological and pharmacological importance, there are several reports in the literature about the synthesis of baclofen (5-8). Although different strategies have been applied

in these reports, the reagents used are expensive (5) or the yield is low (6). In this paper, an alternative approach to the synthesis of Baclofen is described which gives the product with a good yield.

Experimental

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 $60F_{254}$, 0.25mm), and compounds were visualized by UV light of λ= 254nm. IR Spectra were recorded on Perkin-Elmer model 840. ^{1}HNMR spectra were recorded on varian-400 spectrometer.

Preparation of ρ-chloro- β-nitrostyrene

a) ρ-Chlorobenzaldehyde (0.05 mol) and nitromethane (0.05 mol) were mixed in a flask containing methanol (40 ml, 0°C). A solution of sodium hydroxide (2.5 g/5 ml H_2O) was added dropwise into the flask. The reaction mixture was stirred 3 h and then transferred to a cold HCl solution (20%, 40 ml) which caused precipitation. The precipitate was filtered and

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washed with cold water and crystalized by ethanol (mp: 113-114° C, yield: 75%). IR (KBr, cm^{-1}): 3100, 1514, 1338, 1633, 1562, 819.

b) ρ-Chlorobenzaldehyde (0.05 mol) and nitromethane (0.05 mol) with ammonium acetate (0.02 mol) were refluxed in a flask containing glacial acetic acid (20 ml). After 3 h, the reaction mixture was cooled and brought into an ice-water bath. A precipitate thus formed was filtered and crystallized by ethanol (mp: 111-113°C, yield: 79%).

Preparation of diethyl α-[2-nitro-1-(ρ-chlorophenyl)] ethyl malonate

Diethyl malonate (4.2 g) was added to an ethanolic solution of sodium ethoxide (0.4 g sodium in 25 ml dry ethanol). This mixture was then added drop wise into a flask containing ρ-chlorostyrene dissolved in ethanol (4 g/30 ml). After stirring for ½ h, the reaction was made acidic by glacial acetic acid and cooled over an ice bath. The precipitate thus formed was filtered and crystallized by ethanol (mp: 135-137°C, yield: 85%). IR (KBr, cm^{-1}): 1743, 1097, 1558, 1367, 1492, 837.

Preparation of diethyl α-[2-amino-1-(ρ-chlorophenyl)] ethyl malonate

The nitro compound (2.5 g), prepared as above, was mixed with Raney nickle (2.5 g) in an acid-methanol solution (15 ml, 2N HCl; 75 ml methanol) and was brought under hydrogen gas pressure (1 atm) in a reactor. After 30 mins, the mixture was filtered and the filtrate was evaporated to remove the solvent, and was dried (mp: 178-180°C, yield: 84%).

Preparation of baclofen

a) The amino compound, prepared as above, was refluxed with HCl solution (6 M, 50 ml) for 2 h. The solution was then neutralized and cooled. The precipitate, thus formed, was separated and crystallized by water (mp: 206-207°C, yield: 74%). IR (KBr, cm^{-1}): 3400, 1620, 1515, 1490, 830.

b) The nitro compound (2.5g) with Sn powder (3 g) and HCl solution (37%, 10 ml) were refluxed. After 40 mins, the mixture was filtered and the filtrate was neutralized with NaOH solution (2 M). The precipitate, thus formed, was collected (mp: 200-204° C, 39%).
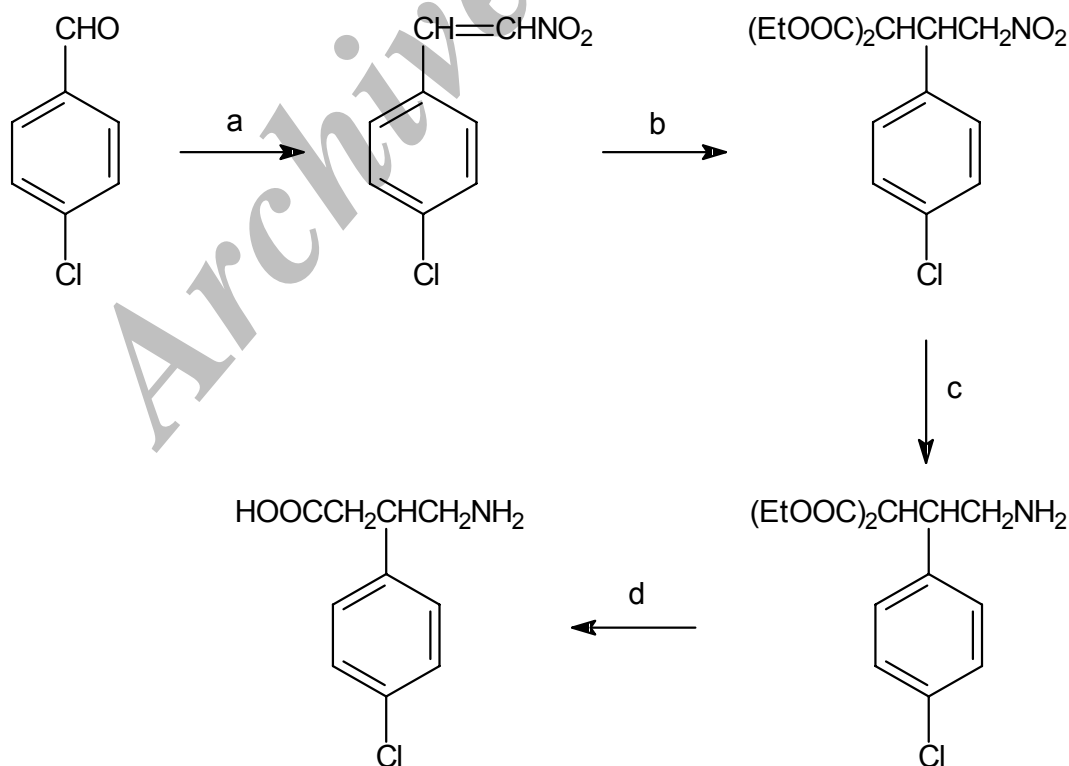
Scheme 1. a) CH$_3$NO$_2$, NaOH, CH$_3$OH, 0°C; b) diethtylmalonate, ethanol, NaOEt,8-10 $^{\circ}$C; c) H$_2$, Raney nickel, CH$_3$OH, room temperature; d) $^-$OH , reflux then H$_3$O$^+$ or H$_3$O$^+$, reflux then $^-$OH.

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Results and discussion

The synthetic strategy for the preparation of baclofen is illustrated in scheme 1. This strategy includes three general steps; 1) aldol condensation, 2) Michael addition, 3) reduction and decarboxylation.

To prepare β-nitrostyrenes two different conditions may be used: 1) a medium with a weak base and high temperature (i.e., ammonium acetate in boiling acetic acid), 2) a medium with a strong base and low temperature (i.e., sodium hydroxide in cold methanol). In our experiments the first condition did not give a good purity of the styrene, but the second one resulted in a good enough purity yield and purity.

The reaction of malonate diethyl ester with the β-nitrostyrene needs a strong base such as sodium alkoxide to make the malonate an active nucleophile which in turn, undergoes a Michael addition reaction. For the reduction of the nitro group several methods may be considered: H_2 (gas) with Raney nickle, HCl with Zn or Fe or Sn powder. When Raney nickel is used, it is necessary to make the medium acidic to prevent lactam formation. The acidic medium also helps the hydrolysis and decarboxylation steps (in a reflux condition). Hydrolysis of the amine compound may also be performed in a basic medium. In order to obtain the final product, baclofen, the pH adjustment of the amino acid is needed.

As a conclusion this paper presents an alternative approach towards the synthesis of baclofen which involves cheap reagents and gives the product with a good yield.

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