Original Article: Synthesis of (±)-Baclofen using Wittig Olefination–Claisen Rearrangement

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ABSTRACT

Baclofen, a lipophilic derivative of GABA (Gamma-Aminobutyric Acid), which acts as an inhibitory neurotransmitter in CNS (Central Nervous System) was synthesized by Witting olefination-Claisen rearrangement protocol. 4-Chlorobenzaldehyde was subjected to Wittig reaction with ((allyloxy)methylene)triphenyl-phosphane to give 1-(2-(allyloxy)vinyl)-4-chlorobenzene which on heating under reflux condition in toluene underwent Claisen rearrangement to give 2-(4-chlorophenyl)pent-4-enal. Aldehyde was reduced to corresponding alcohol 2-(4-chlorophenyl)pent-4-en-1-ol as an important precursor which can be used for the synthesis of Baclofen and different GABA derivatives. Further, tosylation, formation-reduction of azide group and oxidative ozonolysis of terminal double bond yields 4-amino-3-(4-chlorophenyl)butanoic acid (Baclofen) in excellent yield. Therefore, an efficient method was developed for the synthesis of (±)-Baclofen in a simple seven step procedure.

Introduction

Baclofen (Figure 1) is an analog of GABA whichcan cross the blood brain barrier while GABA cannot. Baclofen is a selective and potent agonist for bicuculline-insensitive $GABA_B$ receptors. Baclofen is also used clinically as an antispastic as well as muscle relaxant agent [1]. Baclofen reduces the excitatory effect of active compounds such as barbiturates, benzodiazepine, etc[2,3]. Baclofen is also one of the most promising drugs in the control and treatment of the paroxysmal pain of trigeminal neuralgia [4]. Along with this Baclofen is also used for spasticity of spine without influencing the sedation[5]. Significant increment in gastric acid secretion was also observed in rats through the activation of central cholinergic mechanisms. Baclofen is commercialized in its racemic form [6] though R-enantiomer shows

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biological activity exclusively [7]. The enantiomers of Baclofen differ in their pharmacodynamic and toxicological properties.

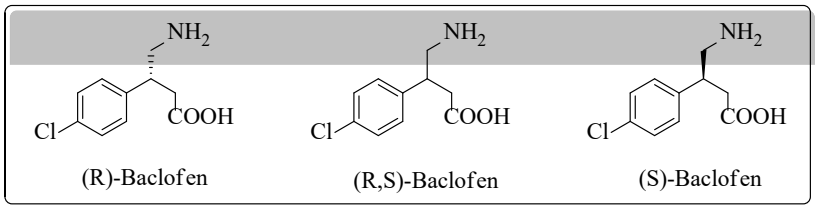


Figure 1. Baclofen Stereoisomer's

Several specific agonists or antagonists at GABA receptor sites have been developed, but 3-(4-chlorophenyl)-4-aminobutyric acid, i.e. Baclofen, is the only clinically useful selective GABAagonists [8]. Baclofen is used in the treatment of paroxysmal pain of trigeminal neuralgia and spasticity of spinal [9].

Enantioselective synthesis of R and/or S form of Baclofen along with their analogues number of methods are reported in the literature. Han *et al.* (2011) used efficient Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to ethyl-γ-phthalimidocrotonate by using bis-sulfoxide ligand for the synthesis of γ-aminobutyric acid (GABA) derivatives [10].Bae *et al.* (2011) used highly enantioselective bio mimetic Michael addition reactions of malonic acid half thioesters (MAHTs) to a variety of nitro olefins to produce (*S*)(+)-Baclofen-HCl salt [11]. Anna *et al.*(2010) developed a enantioselective biocatalytic reduction of β-aryl-β-cyano-α,β-unsaturated carboxylic acids from anaerobic bacteria for (*S*)-Balclofen synthesis[12]. Vasely*et al.*(2008) used a novel organocatalytic highly enantioselective nitrocyclopropanation reaction of α,β-unsaturated aldehydes as a key step for the synthesis of (*S*)-Baclofen [13]. Kozo *et al.*(1998) used Lipase mediated asymmetric acetylation of δ-symmetrical 2-aryl-1,3 propanediols as a key step for the synthesis of (*S*)-Baclofen [14]. Mahendra*et al.* (2015) used asymmetric Michael addition of diethyl malonate to 1-chloro-4-(2-nitrovinyl) benzene in the presence of scandium triflate and spartiene as organo catalyst to produce *R*-(−)-Baclofen [15]. Yang *et al.*(2012) used the Pd-catalyzed asymmetric allylic alkylation (AAA) reaction of nitromethane with (E)-3-(4-chlorophenyl)allyl methyl carbonate (monosubstituted allyl substrates) as a key step for the synthesis of (*R)*- Baclofen [16]. Yongcan*et al.*(2008) used the enantioselective Michael addition reaction of nitromethane to 3-(4-chlorophenyl)-acrylaldehyde (α,β-unsaturated aldehydes) under the catalysis of (*R*)-2-(diphenyl(trimethylsilyloxy)methyl)-pyrrolidine and lithium acetate as additive to make (*R*)-Baclofen[17]. Nikalje*et al.*(2003) synthesized (*R*)-(−)-Baclofen using Ru(II)-(S)-BINAP catalyzed asymmetric hydrogenations of C=C and C=O groups introducing stereogeniccentre into the molecule constitute the key step [18]. Mazzini *et al.*(1997) developed the strategy for the synthesis of (*R*)-Baclofen involved a microbiologically mediated Baeyer Villiger oxidation of the prochiral 3-(4'-chlorobenzyl)-cyclobutanone obtained from 4-chlorostyrene and trichloro acetyl chloride as a key step[19].Fabricio *et al.*(2015) used Michael addition reaction of 1,3-dicarbonyl compound (Meldrum's acid) to nitrostyrene effectively promoted by hydrotalcite [Mg–Al] to afford the respective γ-nitroester through a one pot domino process, which was further converted to (±)-Baclofen [20]. Kallolmay*et al.*(2014) synthesised(±)-Baclofen by suing Suzuki coupling reaction as a key step between mucochloric acid and 4-chlorophenylboronic acid[21]. Chang *et al.*(2006) used MCPBA epoxidation and Baeyer Villiger oxidation reaction for the synthesis of (±)-Baclofen [22]. Ravi *et al.*(2006) synthesized Baclofen using Pd(II)-bipyridine catalyzed conjugative addition of 4-chloroboronic acid as key step [23]. Zhenliang *et al.*(2005) used Rh(II) catalyzed intramolecular C–H insertion of diazoacetamides for the synthesis of (±)-Baclofen [24]. Mohammad *et al.*(2003) used

condensation of β-nitro styrene with diethyl malonate as a key step for the synthesis of (±)-Baclofen [25]. Meng-Yang *et al.*(2003) reported a facile [3+2] annulation reaction as key step between sulfonyl-acetamide derivatives and α-bromo substituted unsaturated alkyl esters to synthesize (±)-Baclofen [26]. Marcos *et al.*(2002) used Heck arylation of N-Boc-3-pyrroline with 4-Chlorophenyl- diazonium tetrafluoroborate using palladium acetate under phosphine free condition to produce (±)-Baclofen [27]. Alcindo *et al.*(2001) introduced 1,4-Michael addition reaction of 2,4,4-trimethyl-2-oxazoline cyanocuprate to the commercially available *p*-chloro-*β*-nitrostyrene for the synthesis of (±)-Baclofen [28]. Fernando *et al.*(1997)synthesized (±)-Baclofen using [2+2] cycloaddition reaction between 4-chlorostyrene and trichloro acetyl chloride [29].

However these methods suffer from many drawbacks such as use of expensive reagents or catalysts and low overall yield. In this context, we report a novel route for the synthesis of (±)-Baclofen.

Experimental Section

Synthesis of 1-(2-(allyloxy)vinyl)-4-chlorobenzene (2)

To a suspension of 4-chlorobenzaldehyde **1** (5 g, 35.56 mmol) and allyloxy methylene triphenylphosphoniumchloride (19.68 g, 53.35 mmol) in dry toluene (60 mL), potassium*tert*-butoxide (4.2 g, 53.35 mmol) was added in small amounts over the period of 10 min. at 0 ^{o}C. Further for 1h, the reaction mixture was stirred at the room temperature. After the completion of reaction (TLC check, 10% ethyl acetate: pet ether), toluene was removed on rotary evaporator under reduced pressure. Water was added and the crude product was extracted thrice with ethyl acetate (3x 25 mL). Water washing was given to the combined organic layer. Organic fractions of ethyl acetate combined was dried with Na_2SO_4 and concentrated on rotary evaporator under reduced pressure. The crude product was further purified by column chromatography using ethyl acetate:pet ether (2:98) as a mobile phase to gave pure allyl vinyl ether **2** as colorless thick liquid. The product in hand was the mixture of *E* and *Z* isomers (12.5 g, 89.2%).

Synthesis of 2-(4-chlorophenyl)pent-4-enal (3)

Tolune (30mL) was added in the isomeric mixture of allyl vinyl ether **2** (12.5 g) and solution was refluxed for 10h at 120 °C. After the completion of reaction (TLC check, 20% ethyl acetate: pet ether), toluene was removed on rotary evaporator under reduced pressure. The crude product aldehyde **3** obtained was the viscous liquid, a mixture of two inseparable enantiomers which was used for the further reaction without any purification (12.4g, 99% yield).

Synthesis of 2-(4-chlorohenyl)pent-4-en-1-ol (4)

Aldehyde **3** (5 g, 25.64 mmol) was dissolved in 5% aqueous methanol (50 mL). Sodium borohydride (0.96 g, 25.64 mmol) was added in the reaction mixture portion wise at 0 °C over a period of 10 min and stirred for 30 min. After completion of reaction (TLC check, 30% ethyl acetate: pet ether), methanol was removed on rotary evaporator under reduced pressure.

Ethyl acetate (20mL) was added in the crude residue followed by water (10 mL). Organic layer was collected separately and aqueous layer was extracted with ethyl acetate (3x10mL). Combined organic was dried over anhydrous sodium bisulphate and concentrated on rotary evaporator under reduced pressure. Column chromatography technique was used for purification with ethyl acetate/pet ether (5:95) as a solvent system to give the alcohol **4** (4.8 g, 96% yield).

Synthesis of 2-(4-chlorophenyl)pent-4-en-1-yl 4-methylbenzenesulfonate(5)

Under a nitrogen atmosphere excess of pyridine (18 g) and catalytic amount of DMAP was added to a solution of alcohol **4** (9 g, 45.91 mmol)in dry DCM at 0 °C. After stirring for 15 min, p-toluenesulfonyl chloride (13.15 g, 68.87 mmol) was added portion wise and stirring was continued for 8h. After completion of reaction (TLC check, 20% ethyl acetate: pet ether),

solvent was removed on rotary evaporator. In the crude product water was added and extraction was done with ethyl acetate (3x10 mL). Na_2SO_4 was used for drying combined organic layer. Dried organic layer was concentrated on rotary evaporator. Further purification was done using column chromatography (hexane/EtOAc, 96:4) to give white solid tosylated compound **5** (15 g, 93%).

Synthesis of 1-(1-azidobut-3-en-2-yl)-4-chlorobenzene (6)

Tosylate**5** (8 g) was dissolved in dry DMF and NaN_3 (4 g) was added. Reaction mixture was stirred for 10h at 60 °C. After completion of reaction (TLC check), reaction mixture was allowed to cool. Water was added and extraction was done with ethyl acetate. The combined organic layer was washed with brine solution and dried with anhydrous Na_2SO_4. Solvent was removed under reduced pressure to get crude product which was purified by column chromatography (hexane/ethyl acetate, 97:3) to give azide**6** as a yellow viscous liquid (4g, 80%).

Synthesis of 4-azido-3-(4-chlorophenyl)butanoic acid (7)

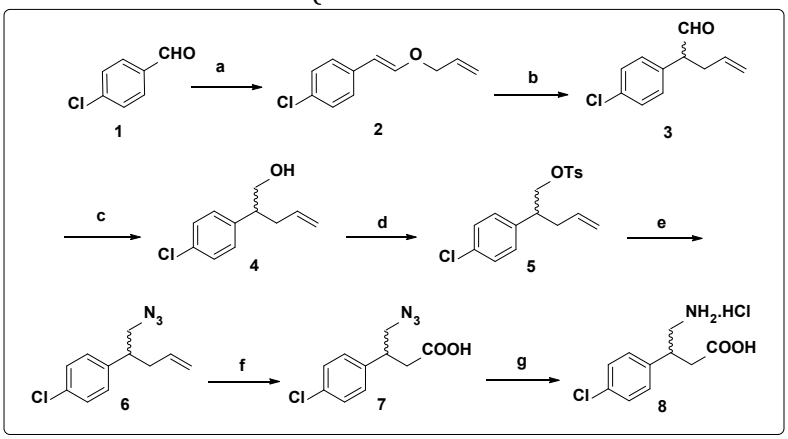
To a stirred solution of azide**6** (1g)in dry DCM, ozone gas was passed at -78 °C for 15 minutes till complete conversion of the reactant into corresponding ozonide. After complete conversion of reactant into ozonide (TLC check), hydrogen peroxide (2 eq.) was added in the reaction mixture to convert ozonide in to corresponding acid. Under reduced pressure, DCM was evaporated on rotary evaporator. Extraction was done by ethyl acetate (2x10 mL). The crude product obtained was purified with base/acid treatment followed by column chromatography (hexane/ethyl acetate, 80:20) to give azido acid **7** as a yellow viscous liquid (0.70g, 65%).

Synthesis of 4-amino-3-(4-chlorophenyl)butanoic acid hydrochloride (8)

A mixture of azido acid **7** (200 mg) in MeOH (15 mL) and 10 % Pd/C (10 mg) was hydrogenated at balloon pressure for 10 h at room temperature. The reaction mixture was filtered off through cilite using vacuum pump. The filtrate was evaporated on rotary evaporator to give (±)-Baclofenascolourless solid (0.149g, 84%). The HCl gas was passed through the solution of residue dissolved in DCM/MeOH for 15-30 minutes. The precipitate thus formed was collected by filtration to obtain salt of (±)-Baclofen hydrochloride **8**.

Result and Discussion

The present strategy for the synthesis of (±)-Baclofen starting from commercially available 4-chlorobenzaldehyde is depicted in **Scheme 1**.



Scheme 1. Reagent and conditions: (a) $ClPh_3PCH_2$-O-$CH_2CH{=}CH_2$, t-BuOK, Toluene, 0 °C, 1h, 90%; (b) Toluene, 120 °C, 10h, 98 %; (c) $NaBH_4$, MeOH, 0 °C, 1h, 96% (d) TsCl, Pyridine, DMAP, DCM, 0 °C,

7h, 93%; (e) NaN_3, DMF, 60 °C, 10h, 80% ; (f) O_3, H_2O_2, DCM, 0 °C, 10 min, 65%; (g) H_2, Pd/C, MeOH, HCl, 84%

The Wittig reagent was powdered and dried under vacuum at 100 °C. Allyloxy-methylene-triphenyl phosphonium chloride salt (1.5 eq.) was treated with 4-chloro benzaldehyde **1** (1 eq.) and t-BuOK (2 eq.) in dry toluene at 0 °C for 1h to get allyl vinyl ether [30-34]. The isomeric mixture of allyl vinyl ether **2** as such was refluxed in toluene to carry the Claisen rearrangement to produce 4-pentenal **3** in enantiomeric form [35]**.** Enantiomeric mixture of aldehyde **3** was reduced to get alcohol **4** using sodium borohydride at 0 °C[35]. Alcohol **4** was protected to achieve **5** using tosyl chloride and excess of pyridine in DCM solvent [36-40].Tosyl ether was heated with sodium azide at 60 °C to produce corresponding azide**6**[41]**.**Double bond from the azide**6** was transformed to corresponding acid functionality using oxidative ozonolysis to get azido acid **7**[42-45].Azido acid **7** was hydrogenated with 10% Pd/C under balloon pressure in presence of hydrogen gas to reduce azide functionality to corresponding amine [41] to gave (±)-Baclofen as product. (±)-Baclofen was treated with HCl to get corresponding hydrochloride salt i.e. (±)-Baclofen hydrochloride **8** as final product in 84% yield.

Conclusion

In summary, we have described a new and efficient method for the synthesis of (±)-Baclofen using Wittig Olefination-Claisen rearrangement as a key step. The overall yield of the reaction is 35%. The synthesis involved easy, reproducible reaction to afford desired product

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Conflict of Interest

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