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Novel Synthesis of Baclofen

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Abstract : Baclofen is a Gama amino Butyric acid (GAMA) agonist used as a skeletal muscle relaxant, it is known to be particularly useful in treating muscle spasticity. We now report the synthesis of Baclofen with patent non-infringing novel route, starting from 4-chlorobenzaldehyde when treated with sodium cyanide gave cyanohydrin with 70% yield. This cyanohydrin on treatment with an oxidizing agent Pyridinium ChloroCromate gave 4-chlorobenzoylcyanide which when further reacted with triphenyl phosphonium ethyl acetate gave a product, which on base hydrolysis followed by catalytic hydrogenation yielded baclofen though in poor yield, the identity of this has been established by mass spectral analysis and confirmed by comparing with standard Baclofen.
Keywords : GABA agonist, Spasticity, 4-Chlorobenzaldehyde, Cyanohydrin, Oxidising agent, Pyridinium chlorochromate, Triphenyl phosphonium ethyl acetate. Hydrolysis, Catalytic hydrogenation, mass spectral analysis and Baclofen.

Introduction

The anticonvulsants are a group of drugs primarily used to treat disorders like epilepsy and they are also effective in regulating mood swings that come with bipolar disorder. They act by suppressing the rapid and excessive release of neurons that start a seizure by rejuvenating neurotransmitters in the central nervous system viz., γ- aminobutyric acid (GAMA) and L – Glutamic acid [(1)]. A number of GABA analogues such as Gabapentin, Pregabalin, Levetracetum and 3 – phenibut are used as anticonvulsant. (S) – pregabalin (S – 3 – aminomethyl – 5- methyl hexanoic acid) has more potent than gabapentin in treating anxiety [(2)] and epilepsy [(3,4)]. The pregabalin synthesis was first reported by Hoeksts et al [(5)] in Warner – Lanbert laboratories. Methods for the synthesis of racemic pregabalin [(6 – 8)] and asymmetric synthesis of pregabalin [(9 – 12)] are reported, pregabalin has also prepared by different methods using 5 – methylhexenoate [(13)], Lossen rearrangement [(14)] involvement in the synthesis of pregabalin, Baclofen and 3 – phenbut using 4 – substituted glutaric anhydride as the starting material repoted.

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Importance of the present work

In an attempt to synthesize Baclofen with patent non – infringing process with novel route and avoiding hazardous chemical like nitromethane

Experimental section:

General methods / Instrument

Solvents and reagents of laboratory grade were obtained from local dealers and were used without further purification IR spectra were recorded on Nicolet avatar 320 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in CDCl3 / DMSO – d_6 at 200 MHz on Bruker. A G spectrometers chemical shifts are reported in δ units down field from TMS as internal standard Mass spectra were recorded using GC-MS-QP2010S (direct probe).

Synthesis of 4-chlorophenyl cyanohydrin (2):

4-chlorobenzaldehyde (10g) was taken in four necked RB flask fitted with condenser and thermometer and charged water (100ml), Sodium cyanide (3.2g) and heated the reaction mass to 80-85℃ for three hours. Reaction monitored with TLC using Ethyl acetate: hexane as mobile phase. After the reaction completion, carefully added concentrated hydrochloric acid (Note: this part performed in a good fume hood) then extracted with ethyl acetate, water wash to the ethyl acetate layer, and dried with sodium Sulphate and concentrated under vacuum, hexane added, filtered the mass to give compound (2) of 70% yield (8.0g), M. P.85-90℃; ^{1}H NMR ($CDCl_3$); δ (ppm): 4.5(d, 1H, J=5.8Hz), 5.8(d, 1H, J=5.8Hz) 7.4(d, 2H, J=8.6HZ), 7.8(d ,2H, J=8.6Hz)

Synthesis of 4-chlorobenzoyl cyanide (3):

4-chlorocyanohydrin (2) (3.0g) was taken in two necked RB Flask fitted with thermometer, charged methylene dichloride (MDC) (20ml) and pyridinium chlorochromate (4.0g) stirred at 25-30℃ for 24 hours, added water (20ml) and separated the organic layer. evaporated off MDC under vacuum, hexane added and filtered the product (3) of 25.5% yield. 0.5g, ^{1}H NMR ($CDCl_3$); δ (ppm); 7.5(d, 2H, J=8.6Hz), 7.9(d, 2H, J=8.6Hz)

Synthesis of compound (4)

In a single neck RB flask, Bromo ethyl acetate (0.4g), triphenyl phosphine (0.6g) and toluene (10ml) were taken and refluxed for 6 hours, filtered and washed the solid with toluene and this solid was taken in fresh single neck RB flask and to which charged MDC and 4-chlrobenzoyl cyanide (3) (0.4g) at 25-30℃, then added potassium tertiary butoxide (0.65g) slowly over a 10 minutes and stirred for 6 hours, the reaction mass was subjected to silica gel column chromatography to get compound (4) of 12.5% yield; 0.07g, ^{1}H NMR ($CDCl_3$); δ (ppm); 1.15(t, 3H, J=7.0Hz), 4.14(q, 2H, J=7.0 Hz), 6.48(S, 1H), 7.4(d, 2H, j= 8.6Hz), 7.8(d, 2H, J=8.6Hz).

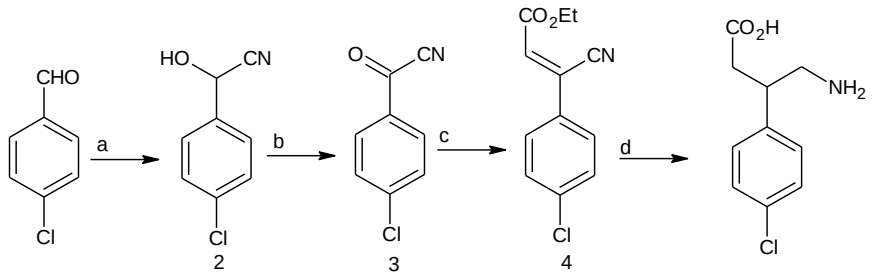
Synthesis of Baclofen (1):

To the above compound(4) (0.06g) in methanol (10ml) was added potassium hydroxide (0,3g) stirred for 6 hours, concentrated the reaction mass under vacuum, acidified with hydrochloric acid extracted with MDC, organic layer was concentrated to obtain product (0.05g) and which was dissolved in methanol (30ml) and to which was added(0.01g) of Raney – nickel catalyst and hydrogenated under 3.0 Kg pressure and filtered Raney – nickel catalyst, filtrate concentrated under vacuum yielded Baclofen (1) of 18.8% 0.01g, M.P. 196-198℃, MS;213(M^+)

Results and Discussion

The synthesis of Baclofen started with 4 – chlorobenzaldehyde which on treatment with sodium cyanide gave cyanohydrin which is a addition product with 70% yield, this on treatment with oxidising agent pyridinium chlorochromate gave 4 – chloro benzoyl cyanide which upon treatment with triphenyl phosphonium ethyl acetate gave product, this on base hydrolysis followed by catalytic hydrogenation led to Baclofen (I) in poor yield, it was characterized by comparison on TLC (Co – TLC) with standard baclofen and by melting point and mixed melting point and by mass spectral data, the Rf value of the product in TLC system (Formic acid: water:

Acetone: Chloroform: Methanol: 0.5:0.5:2.0:1.0:1.0) was found to be 0.65. All attempts by changing reaction conditions like solvent and temperature did not help in improving the yields of the product. We plan in future to modify witting reaction conditions by using phosphonate stabilized carbanions with electron withdrawing substituents viz., an ylide reacting triethyl phosphate with bromomethyl acetate



Scheme 1.0

Scheme 1.0: reagents and conditions: (a) sodium cyanide, water, 80 – 85^{0}c (b) pyridinium chlorochromate, 25 – 30^{0}c (c) bromoethylacetate, triphenylphosphine, Toluene, reflux for 3 hours, filtered and solid taken in MDC, potassium ter – butoxide (d) Potassium hydroxide in methanol, 25 – 30^{0}c and hydrogenation inpresence of Raney – nickel catalyst

Conclusion

Synthesised Baclofen by novel method starting from 4 – chlorobenzaldehyde which when treated with Sodium cyanide gave cyanohydrin with 70% yield. This cyanohydrin when treated with oxidising agent Viz., Pyridinium chlorochromate gave 4 – Chlorobenzoyl cyanide which upon treatment with triphenyl phosphonium ethyl acetate gave product, which on base hydrolysis followed by catalytic hydrogenation led to the formation of Baclofen (1) in poor yield.

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