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# Improved process for the preparation of (±) 4-amino-5-hexenoic acid

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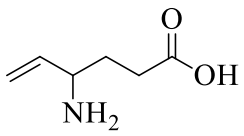
# Improved process for the preparation of (±) 4-amino-5-hexenoic acid

**Abstract:**

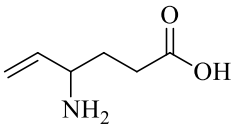
The present invention relates to an improved process for the preparation of (±) 4-amino-5-hexenoic acid, represented by the following structural formula.



Formula-1

**Background of the Invention:**

Vigabatrin is chemically known as (±) 4-amino-5-hexenoic acid represented by the following structural formula.



Formula-1

Vigabatrin is an irreversible mechanism-based inhibitor of gamma-aminobutyric acid aminotransferase (GABA-AT), the enzyme responsible for the catabolism of GABA. Inhibition of GABA-AT results in increased levels of GABA in the brain. Vigabatrin is a racemic compound, and its (S)-enantiomer is pharmacologically active.

Vigabatrin is used as an adjunctive treatment in epilepsy and related syndromes, but as monotherapy for the treatment and/or prophylaxis of West syndrome. It is commercially known as Sabril® in Belgium, Canada, Mexico, Switzerland, USA and UK, and Sabrilex® in Denmark.

(±) 4-amino-5-hexenoic acid was disclosed in US3960927 A and this patent also discloses process for the preparation of (±) 4-amino-5-hexenoic acid by the reduction of 4-amino-5-yne-hexanoic acid.

**Detailed description of the Invention:**

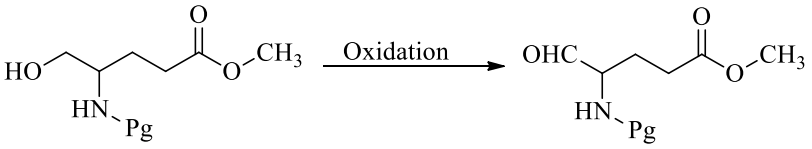
As used herein the term “suitable solvent” used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, toluene, pentane, cycloheptane, methyl cyclohexane, m-, o-, or p-xylene, and the like; “ether solvents” such as dimethoxy methane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene

glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, dimethoxy ethane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; "polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyro nitrile and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol, monoethyl ether, cyclohexanol, benzyl alcohol or glycerol and the like; "polar solvents" such as water or mixtures thereof.

The "suitable base" as used in the present invention is selected from inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia; and organic bases such as "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; triethyl amine, methyl amine, ethylamine, 1,8-diaza bicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithiumdiiso propylamide (LDA), Sodium bis(trimethylsilyl)amide (NaHMDS), n-butyl lithium, tribenzylamine, isopropyl amine, diisopropylamine, diisopropylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylamino pyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methyl imidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

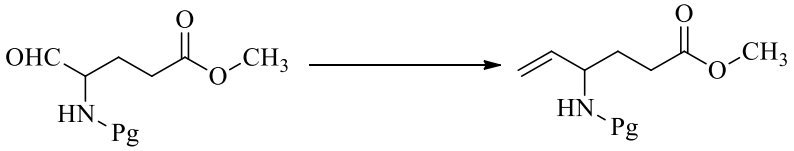
In the first embodiment, the present invention provides a process for the preparation of Vigabatrin of formula-1, which comprises:

a) oxidation of compound of general formula-5 with suitable oxidizing agent in the presence of suitable base and in a suitable solvent to provide compound of general formula-4;




Formula-5 Formula-4

b) converting compound of general formula-4 to compound of general formula-3; and




Formula-4 Formula-3

c) converting compound of general formula-3 to Vigabatrin of formula-1.

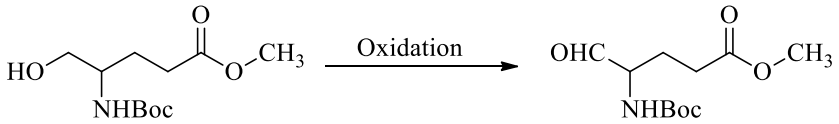
wherein "Pg" is selected from nitrogen protecting group such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc), p-Methoxybenzyl ethers (PMB), methyloxycarbonyl, acetoxy carbonyl, propoxycarbonyl, acetyl, propanoyl, iso-butyryl, tert-butyryl, t-butylacetyl, pivaloyl, benzoyl, trimethylsilyl, ter-butyldimethylsilyl, methane sulphonyl, p-tolylsulphonyl, 2-nitrophenylsulfenyl; urea; urethane; nitroso; nitro and the like.

In the process of the first embodiment, the suitable solvent used in step-a) is selected from alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polaraprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof; the suitable base used in step-a) is selected from inorganic base or organic base.

In the process of the first embodiment, the suitable oxidizing agent used in step a) is selected from sodium hypochlorite (NaOCl), calcium hypochlorite ($Ca(OCl)_2$), sodium bromate ($NaBrO_3$), Dess-Martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (Swern oxidation), trichloroisocyanuric acid, TEMPO, pyridiniumchlorochromate (PCC), potassium dichromate, manganese dioxide, oxone, chromium trioxide, N-chlorosuccinimide/dimethylsulfide, peracids such as metachloro perbenzoic acid, performic acid, peracetic acid, perbenzoic acid and the like.

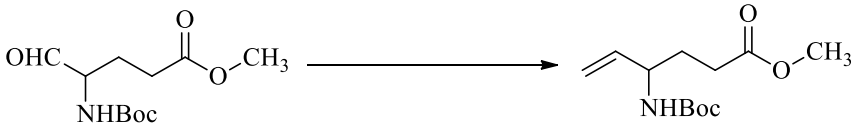
In the first aspect of the first embodiment, the present invention provides a process for the preparation of Vigabatrin of formula-1, which comprises:

a) oxidation of compound of formula-5a with oxalyl chloride in dimethyl sulfoxide in the presence of triethylamine and dichloromethane to provide compound of formula-4a;




Formula-5a Formula-4a

b) reacting compound of formula-4a with methyltriphenylphosphonium bromide in the presence of sodium bis(trimethylsilyl)amide and THF to provide compound of formula-3a; and

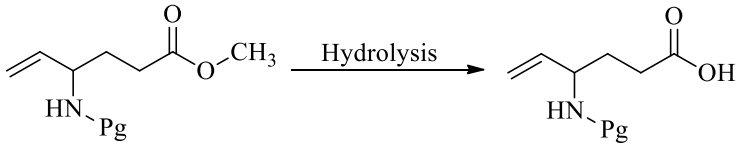



Formula-4a Formula-3a

c) converting compound of formula-3a to Vigabatrin of formula-1.

In the second embodiment, the present invention provides a process for the preparation of Vigabatrin of formula-1, which comprises:

a) hydrolysis of compound of general formula-3 in the presence of suitable base in a suitable solvent to provide compound of general formula-2; and




Formula-3 Formula-2

b) deprotection of compound of general formula-2 in the presence of suitable deprotecting agent in a suitable solvent to provide Vigabatrin of formula-1.


Formula-2 Vigabatrin

wherein "Pg" is defined above.

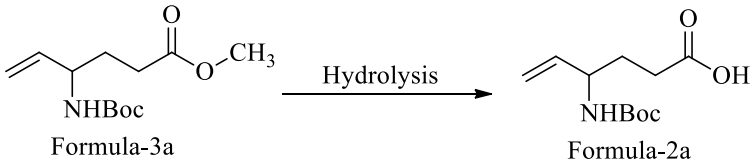
In the process of the second embodiment, the suitable solvent used in step-a) and step-b) is selected from alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polaraprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof; the suitable base used in step-a) is selected from inorganic base or organic base.

In the process of the second embodiment, the suitable deprotecting agent used in step-b) is selected trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid,

trifluoromethanesulfonic acid, trimethylsilylchloride, hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, acetic acid and mixtures thereof.

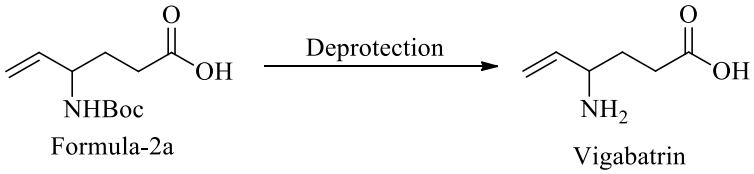
In the first aspect of the second embodiment, the present invention provides a process for the preparation of Vigabatrin of formula-1, which comprises:

a) hydrolysis of compound of formula-3a in the presence of sodium hydroxide and methanol to provide compound of formula-2a; and




Formula-3a Formula-2a

b) deprotection of compound of formula-2a in the presence of HCl in 1,4-dioxane to provide Vigabatrin of formula-1.




Formula-2a Vigabatrin

Vigabatrin obtained according to the present invention can be purified using a suitable solvent selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

Vigabatrin produced by the present invention can be further micronized or milled in conventional techniques to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball milling, roller milling and hammer milling, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The invention also encompasses pharmaceutical compositions comprising Vigabatrin of the present invention. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The process described in the present invention is demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

**Examples:**

**Example-1: Preparation of 2-amino-5-methoxy-5-oxopentanoic acid hydrochloride.**

Methanol (1000.0 ml) was added to DL-glutamic acid (200.0 gm) at 25-30ºC and stirred for 20 minutes. Trimethylsilyl chloride (210.0 ml) was slowly added to the mixture at 25-30ºC and stirred for 2 hours. Distilled off the solvent completely from the mixture at below 45ºC under vacuum and co-distilled with ethyl acetate. Acetone (600.0 ml) was added to the obtained compound at 25-30ºC and stirred for 20 minutes. Cooled the mixture to 0-5ºC and stirred for 2 hours. Filtered the sold, washed with acetone and dried to get the title compound.
Yield: 100.0 gm.

**Example-2: Preparation of 2-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid.**

Water (600.0 ml) and 1,4-dioxane (600.0 ml) was added to 2-amino-5-methoxy-5-oxopentanoic acid hydrochloride (150.0 gm) at 25-30ºC. Cooled the mixture to 15-20ºC. Potassium carbonate solution was slowly added to the mixture at 15-20ºC. Cooled the mixture to 0-5ºC. Di-tert-butyl dicarbonate (198.7 gm) was slowly added to the mixture at 0-5ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 11 hours. Distilled off the solvent completely from the mixture at below 45ºC under vacuum. Ethyl acetate (300.0 ml) was added to the obtained compound at 25-30ºC and stirred for 10 minutes. Layers were separated. Dichloromethane (750.0 ml) was added to the aqueous layer at 25-30ºC. Layers were separated. Hydrochloride solution was added to the aqueous layer and extracted with dichloromethane. Combined the total organic layer and washed with water at 25-30ºC. Distilled off the solvent completely from the organic layer at below 45ºC under vacuum to get the title compound. Yield: 180.0 gm.

**Example-3: Preparation of methyl 4-((tert-butoxycarbonyl)amino)-5-hydroxypentanoate of Formula-5a.**

2-((tert-butoxycarbonyl)amino)-5-methoxy-5-oxopentanoic acid (50.0 gm) was dissolved in methyl tert-butyl ether (200.0 ml) at 25-30ºC and stirred for 20 minutes. Cooled the mixture to -20 to -15ºC. N-Methylmorpholine (22.09 ml) and ethyl chloroformate (19.05 ml) were added to the mixture at -20 to -15ºC and stirred for 15 minutes. Filtered the mixture through hyflow bed and washed the hyflow bed with methyl tert-butyl ether. Sodium borohydride (10.90 gm) was added to the filtrate at -20 to -15ºC and stirred for 10 minutes. Methanol (125.0 ml) was slowly added to the mixture at -20 to -15ºC and stirred for 1 hour.

Hydrochloride solution was slowly added to the mixture at -20 to -15ºC. Water (250.0 ml) was added to the mixture at 25-30ºC and stirred for 10 minutes. Layers were separated and aqueous layer extracted with methyl tert-butyl ether. Combined the total organic layer and washed with sodium chloride at 25-30ºC. Distilled off the solvent completely from the organic layer at below 45ºC under vacuum to get the title compound. Yield: 52.0 gm.

**Example-4: Preparation of methyl 4-((tert-butoxycarbonyl)amino)hex-5-enoate of Formula-3a.**

Dichloromethane (500.0 ml) and dimethyl sulfoxide (84.0 ml) were charged into a round bottom flask at 25-30ºC. Cooled the mixture to -75 to -70ºC. Oxalyl chloride (52.2 ml) was slowly added to the mixture at -75 to -70ºC and stirred for 30 minutes. Pre-prepared compound of formula-5a (50.0 gm) and dichloromethane (100.0) solution was slowly added to the mixture at -75 to -70ºC and stirred for 90 minutes. Triethylamine (222.0 ml) was slowly added to the mixture at -75 to -70ºC and stirred for 10 minutes. Water (500.0 ml) was added to the mixture at -75 to -70ºC and stirred for 5 minutes. Layers were separated and aqueous layer extracted with dichloromethane. Combined the total organic layer and washed with water at 25-30ºC. Distilled off the solvent completely from the organic layer at below 40ºC under vacuum to get the compound of formula-4a.

Methyltriphenylphosphonium bromide (75.0 gm) and tetrahydrofuran (500.0 ml) were charged into a round bottom flask at 25-30ºC and stirred for 5 minutes. Sodium bis(trimethylsilyl)amide (120.0 ml) was slowly added to the mixture at 25-30ºC and stirred for 1 hour. Cooled the mixture to -10 to -5ºC. Compound of formula-4a was slowly added to the mixture at -10 to -5ºC and stirred for 30 minutes. Filtered the mixture through hyflow bed and washed the hyflow bed with tetrahydrofuran. Water (500.0 ml) was added to the filtrate at 0-5ºC and stirred for 5 minutes. Layers were separated and aqueous layer extracted with ethyl acetate. Combined the total organic layer and washed with water at 25-30ºC. Distilled off the solvent completely from the organic layer at below 40ºC under vacuum to get the title compound. Yield: 100.0 gm.

**Example-5: Preparation of Vigabatrin of Formula-1.**

Methanol (60.0 ml) was added to compound of formula-3a (12.0 gm) at 25-30ºC and stirred for 20 minutes. Cooled the mixture to 0-5ºC. Sodium hydroxide (2.36 gm) was slowly added to the mixture at 0-5ºC and stirred for 30 minutes. Raised the temperature of the mixture

to 25-30ºC and stirred for 3 hours. Distilled off the solvent completely from the mixture at below 50ºC under vacuum to get the compound of formula-2a.

1,4-Dioxane (48.0 ml) was added to the compound of formula-2a at 25-30ºC and stirred for 10 minutes. Cooled the mixture to 0-5ºC. Hydrochloride solution was slowly added to the mixture at 0-5ºC. Raised the temperature of the mixture to 55-60ºC and stirred for 4 hours. Distilled off the solvent completely from the mixture at below 50ºC under vacuum. Water (36.0 ml) and ethyl acetate (36.0 ml) was added to the obtained compound at 25-30ºC and stirred for 15 minutes. Layers were separated. Cooled the aqueous layer to 5-10ºC. Sodium hydroxide solution was added to the aqueous layer at 5-10ºC and stirred for 15 minutes. Distilled off the solvent completely from the mixture at below 50ºC under vacuum and co-distilled with isopropanol. To the obtained compound dissolved in water (12.0 ml) and isopropanol (96.0 ml) at 25-30ºC. Heated the mixture to 70-75ºC and stirred for 30 minutes. Filtered the mixture and washed with isopropanol at 25-30ºC. Cooled the filtrate to 0-5ºC and stirred for 3 hours. Filtered the solid, washed with isopropanol and dried to get the title compound.

Yield: 2.8 gm.

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