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A process for the preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone

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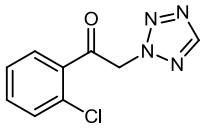
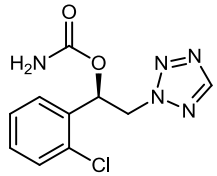
Field of the invention:

The present invention relates to an improved process for the preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone compound of formula-2 and its conversion to Cenobamate of formula-1 or its pharmaceutically acceptable salts.



Formula-2 (2N)

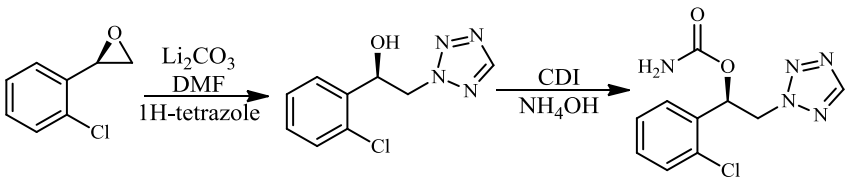


Formula-1

Background of the invention:

Cenobamate is chemically known [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl) ethyl] carbamate. Cenobamate is approved under the brand name Xcopri® for the treatment of partial-onset seizures in adult patients.

Cenobamate is disclosed in US 7598279 B2. This patent discloses a process for the preparation of Cenobamate comprises reacting the (R)-2-chlorostyrene oxide of Formula–6 with 1H-tetrazole in dimethylformamide in presence of lithium carbonate to obtain (R)-1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanol of Formula-5 followed by reacting with 1,1′-carbonyl diimidazole and ammonium hydroxide to obtain crude Cenobamate and obtained Crude Cenobamate is purified by silica gel column chromatography. The process is depicted in the below as scheme-1:



Formula-6 Formula-5 Cenobamate

Scheme-1

The major disadvantages associated with the process disclosed in US 7598279 is the usage of (R)-2-chlorostyrene oxide is commercial not available and also terminal epoxides are not stable. Further, the purification of crude Cenobamate column purification is required. Thus requires more labor and extreme care to use, which makes the process commercially not viable.

US 8501436 B2 patent discloses a process for the preparation of Cenobamate comprises reacting the 2-bromo-1-(2-chlorophenyl)ethanone of Formula–V with 1H-tetrazole in acetonitrile in presence of potassium carbonate to obtain 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of Formula-VI, followed by reduction by chemical asymmetric reduction with a chiral borane reductant of (-)-B-chlorodiisopinocampheylborane or asymmetric catalytic transfer hydrogenation with formic acid triethylamine or isopropanol-inorganic base in the presence of chloro{(1S,2S)-(+)-amino-1,2-diphenylethyl](4-toluenesulfonyl)amido}(p-cymene)ruthenium(II) and also (R)-selective reduction is achieved by biological asymmetric reduction that is carried out in a buffer containing the 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of Formula-VI, a microbial strain capable of producing oxidoreductase that is selected from the group consisting of Candida *parapsilosis*, Pichia *jadinii* and Rhodotorula *mucilaginosa*; and a co-substrate.

US 10611737 B2 patent describes the preparation 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of formula 2 comprises a step of reacting 2 -bromo -2 -chloroacetophenone with a salt of a tetrazole.

There is a need for methods of making Cenobamate or its intermediates that can ameliorate certain drawbacks in prior art.

Brief description of the invention:

The first embodiment of the present invention provides a process for the preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of formula-2.

The second embodiment of the present invention provides crystalline form of Cenobamate of formula-1.

The third embodiment of the present invention provides a process for the preparation of crystalline form of Cenobamate of formula-1.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD pattern of crystalline form of Cenobamate.

Detailed description of the invention:

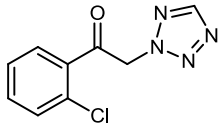
The “solvent” used in the present invention can be selected from but not limited to “hydrocarbon solvents” such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; “ether solvents” such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and mixtures thereof; “ester solvents” such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof; “polar-aprotic solvents” such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and mixtures thereof; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and mixtures thereof; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and mixtures thereof; “alcohol solvents” such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and mixtures thereof; “polar solvents” such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The term "pharmaceutical compositions" or "pharmaceutical formulations" used in the present invention include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

The term “pharmaceutically acceptable excipients” selected from but not limited to binders, diluents, disintegrants, surfactants and lubricants. Suitable binders that can be include polyvinylpyrolidone, copovidone, starches such as pregelatinized starch, cellulose derivatives such as hydroxypropylmethyl cellulose, ethylcellulose, hydroxypropylcellulose and carboxymethylcellulose, gelatine, acacia, agar, alginic acid, carbomer, chitosan, dextrates, cyclodextrin, dextrin, glycerol dibehenate, guargum, hypromellose, maltodextrin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, sodium alginate, sucrose, mixtures thereof; suitable diluents that can be include anhydrous lactose, lactose monohydrate,

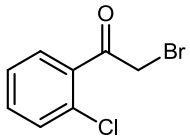
modified lactose, dibasic calcium phosphate, tribasic calcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, maize starch, pregelatinized starch, calcium carbonate, sucrose, glucose, dextrates, dextrins, dextrose, fructose, lactitol, mannitol, sorbitol starch, calcium lactate or mixtures thereof; suitable disintegrants that can be include magnesium aluminometa silicate (or magnesium aluminum silicate), starch, pregelatinized starch, sodium starch glycolate, crospovidone, croscarmellose sodium, low-substituted hydroxypropyl cellulose, alginic acid, carboxy methyl cellulose sodium, sodium alginate, calcium alginate and chitosan; suitable lubricants that can be include (but are not limited to) magnesium stearate, stearic acid, palmitic acid, talc, and aerosil. Suitable surfactants that can be include (but are not limited to) polysorbate 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxy-propylene copolymer and sodium lauryl sulphate; beta-cyclodextrin include (but are not limited to) sulfobutylalkyl ether-beta-cyclodextrin, betadex-sulfobutylether sodium, or hydroxypropyl-beta-cyclodextrin.

First embodiment of the present invention provides a process for the preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of formula-2



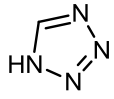
Formula-2

which comprises reacting 2-bromo-2-chloroacetophenone of formula-3



Formula 3

with 1*H*-tetrazole of formula-4



Formula 4

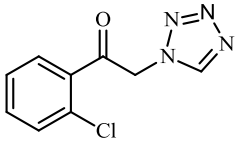
in presence of a base in an ester solvent optionally in the presence of catalytic amount of dimethylformamide.

Wherein, dimethylformamide is used in less than about 0.5 times with respect to 2-

bromo-1-(2-chlorophenyl)ethanone of formula-3; base in 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; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; ammonia; and organic bases such as triethyl amine, diethylamine, trimethylamine, methyl amine, ethyl amine, tripropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithium dioisoporpylamide (LDA), n-butyl lithium, tribenzylamine, isopropyl amine, diisopropylamine (DIPA), diisopropylethylamine (DIPEA), N-methylmorpholine (NMP), N-ethylmorpholine, piperidine, dimethylaminopyridine (DMAP), morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methylimidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof; wherein ester solvent in is selected from methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof.

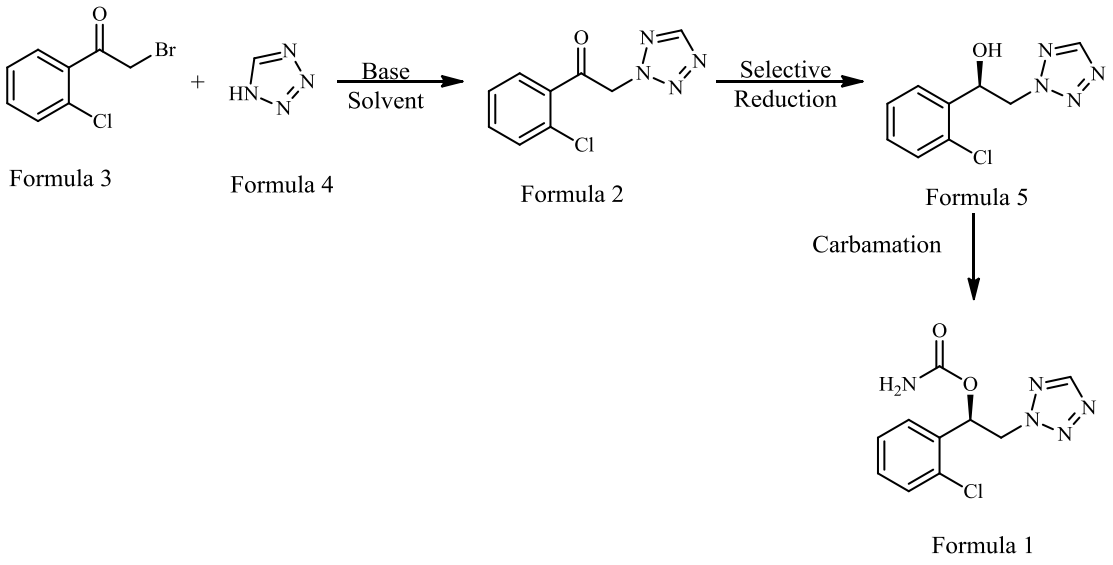
The first aspect of first embodiment further comprises converting 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone of formula 2 to Cenobamate of formula 1. The conversion can be done by the process known in the literature or by the process described in the present application.

The second aspect of first embodiment further comprises the structure of 1N-ketone impurity as follows:



1N-Keto impurity

The first embodiment of present invention is schematically represented as follows in Scheme-2.



Scheme-2

In the given scheme, the compound of formula-2 can be reduced to obtain a chiral alcohol of formula-5 using various methods to introduce chirality. These methods include employing chemical asymmetric hydride reducing agents such as chiral borane agents, conducting asymmetric catalytic hydrogenation in presence of chiral auxiliary, or by employing ketoreductase enzymes.

The second embodiment of the present invention provides crystalline form of Cenobamate of formula-1.

The first aspect of the second embodiment provides crystalline form of Cenobamate characterized by one or more of the following characteristics:

i) PXRD (powder X-Ray diffraction) pattern having peaks at about 12.4°, 13.5°, 14.8° and 26.5° 2θ ± 0.2° 2θ; or

ii) PXRD (powder X-Ray diffraction) pattern having peaks at about 10.1°, 12.4°, 13.5°, 14.8° and 26.5° 2θ ± 0.2° 2θ; or

iii) PXRD pattern as illustrated in Figure 1.

The second aspect of second embodiment provides the use of crystalline form of Cenobamate of formula-1 of the present invention for the preparation of various pharmaceutical formulations.

The third aspect of second embodiment provides pharmaceutical composition comprising crystalline form of Cenobamate of formula-1 obtained according to the present invention and at least one pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Third embodiment of the present invention provides a process for the preparation of crystalline form of Cenobamate comprising:

a) dissolving Cenobamate of formula-1in a first solvent,

b) optionally combining with a second solvent and

c) isolating the crystalline form of Cenobamate.

Wherein dissolving Cenobamate in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; the first solvent in step-a) is selected from ketone solvents, ester solvents, nitrile solvents, alcohol solvents and chloro solvents and/or a mixtures thereof; second solvent in step-b) is selected from hydrocarbon solvents, water and/or a mixture thereof; wherein isolating crystalline form of Cenobamate in step c) is done by removal of solvent using known techniques like decantation, filtration by gravity or suction, centrifugation, concentration, or other techniques specific to the equipment used, and optionally washing with a solvent.

HPLC Method of Analysis:

Cenobamate and its related substances were analyzed by HPLC with the following chromatographic conditions:

Apparatus: A liquid chromatograph is equipped with variable wavelength UV Detector.

Column: Kromasil- C18, 250 x 4.6 mm, 5 µm (Make & P. No: Nouryon & M05CLA25);

Wavelength: 210 nm;

Column temperature: 25°C;

Injection volume: 5 µL;

Elution: Gradient;

Diluent: Acetonitrile: Water (1:1) v/v; Needle wash: Diluent.

Buffer Preparation:

i) Accurately transfer 1000 ml of milli-Q water into a suitable cleaned and dry beaker.

ii) Transfer accurately about 2 mL of orthophosphoric acid (85%) into a beaker containing 1000 mL of milli-Q water and mix well.

iii) Filter the above solution through 0.22 µm polyvinylidine fluoride membrane filter paper and sonicate about of 2-3 minutes to degas it.

Mobile phase-A: Buffer 100%;

Mobile phase-B: Acetonitrile: Buffer: Methanol (70:30 v/v)

The crystalline form of Cenobamate of the present invention is characterized by unit cell parameters approximately equal to the following:

Cell dimensions:

Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.078(4)
b/Å	11.108(4)
c/Å	14.194(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1273.7(9)
Z	4
ρ_{calc}g/cm^3	1.396

Single crystals of Cenobamate was selected in a cryloop with mineral oil on a Bruker APEX-IV Photon II diffractometer. The crystals were kept at 273.15K during the data collection. Using Olex2 (Dolomanov, O.V., Bourhis, L.,J., Giledea, R.J. Howard, J.A.K and Puschman, H. (2009), J. Appl. Cryst. 42, 339-341), the structure was solved with the XT (Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8) structure solution program using Intrinsic Phasing and refined with

XL (Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122) refinement using Least Square minimization.

Cenobamate of formula-1 obtained according to the present invention and one or more pharmaceutically acceptable carriers is indicated for the treatment of partial-onset seizures in adult patients.

The compound of formula-1 produced by process of the present invention is having purity of greater than about 99%, preferably greater than about 99.5%, more preferably greater than about 99.7%, most preferably greater than about 99.8% by HPLC {High Performance Liquid Chromatography}.

Cenobamate produced by the processes of the present invention can be further micronized or milled to get 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 includes but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

In an embodiment of the present invention, Cenobamate having particle size distribution characterized by: D[90] value is greater than about 330 µm. Preferably D[90] value is more than about 350 µm.

HPLC method of analysis for the Cenobamate & its intermediates of the present invention can be carried out by known techniques.

PXRD Method of Analysis:

The PXRD analysis of compounds of the present invention was carried out by using BRUKER/D8 ADVANCE X-Ray diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

The best mode of carrying out the present invention was illustrated by the below

mentioned examples. These examples are provided as illustration only and hence should not be considered as limitation of the scope of the invention.

Examples:

Example 1: Preparation of 2 -bromo -2 –chloroacetophenone

Bromine (434.14 g) was lot wise added to the mixture of 1-(2-chlorophenyl)ethanone (300 g) and acetic acid (1500 ml) at 20-25°C, raised the temperature to 25-30°C and stirred at the same temperature. Water (3000 ml) and sodium sulfite (420 g) were added to reaction mixture at 30-35°C and stirred at the same temperature. Toluene added to the reaction mixture at 30-35°C, separated the both organic and aqueous layers and aqueous layer is extracted with toluene. Combined the organic layers and washed with water, followed by with aqueous sodium carbonate solution and further with aqueous sodium chloride solution. Solvent was completely distilled off from organic layer to get the title compound.

Yield: 452.5 g; Purity by HPLC: 94.89%.

Example 2: Preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone [formula 2]

Potassium carbonate (7.10 g) and 1H-tetrazole (3.3 g) were added to the mixture of 2 -bromo -2 –chloroacetophenone (10 g) and isopropyl acetate (100 ml) at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered solid, washed with isopropyl acetate and distilled off solvent to get the title compound.

Yield: 8.6 g; Purity by HPLC: 64.58%; 29.09% (1N-ketone impurity).

Example 3: Preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone [formula 2]

Potassium carbonate (7.10 g) and 1H-tetrazole (3.3 g) were added to the mixture of 2 -bromo -2 –chloroacetophenone (10 g) and n-butyl acetate (100 ml) at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered solid, washed with n-butyl acetate and distilled off solvent to get the title compound.

Yield: 9.0 g; purity by HPLC of 2N-ketone: 66.84% and 1N-ketone: 25.33%.

Example 4: Preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone [formula 2]

Potassium carbonate (106.5 g) and 1H-tetrazole (49.5 g) were added to the mixture of 2 -bromo -2 –chloroacetophenone (150 g) and n-butyl acetate (1500 ml) at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered solid and washed with n-butyl acetate. Aqueous sodium thiosulfate solution was added to

obtained solid compound, separated the both organic layers and organic layer was washed with aqueous sodium chloride solution. Carbon treatment was given to organic layer and washed with n-butyl acetate. Distilled off solvent and further co-distilled with methyl tertiary butyl ether. Methyl tertiary butyl ether added to above obtained compound at 25-30°C, heated to 50-55°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with methyl tertiary butyl ether and distilled off solvent completely and further co-distilled with isopropanol. Obtained compound is recrystallized using isopropanol to get the title compound.

Yield: 55 g; Purity by HPLC: 98.74%.

Example 5: Preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone [formula 2]

Potassium carbonate (31.9 g), 1H-tetrazole (13.50 g) and diemthylformamide (4.5 ml) were added to the mixture of 2 -bromo -2 –chloroacetophenone (45 g) and n-butyl acetate (450 ml) at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered solid and washed with n-butyl acetate. Water added to the obtained filtrate, separated the both organic and aqueous layers. The organic layer was washed with water and followed by aqueous sodium chloride solution. Distilled off the solvent from organic layer and co-distilled with methyl tertiary butyl ether. Methyl tertiary butyl ether (270 ml) added to above obtained compound at 25-30°C, heated to 50-55°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with methyl tertiary butyl ether and distilled off solvent completely and further co-distilled with isopropanol. Isopropanol (90 ml) added to the obtained compound at 25-30°C, heated to 60-65°C and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Water (11.25 ml) added to mixture at 25-30°C and stirred at the same temperature. Cooled the mixture to 10-15°C and stirred. Filter the solid, washed with mixture of isopropanol and water and dried to get the title compound.

Yield: 18.8 g; Purity by HPLC: 94.86%.

Example 6: Preparation of (R)-1-(2-chlorophenyl)-2-(1,2,3,4-tetrazol-2-yl)ethan-1-ol for [formula-5]

Preparation of buffer solution: Triethanolamine (54.01 g) is slowly added to mixture of water (988 ml) and magnesium sulfate heptahydrate (0.24 g) at 25-30°C and stirred at the same temperature.

Preparation of stock solution: Mixture of isopropanol (702 ml) and buffer solution (468 ml) stirred at 25-30°C.

Mixture of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone (130 g), isopropanol (1430 ml) and buffer solution (390 ml) heated to 55-60°C. Beta NADP monosodium salt (0.195 g), optimized Ketoreductase Enzyme (1.95 g) and buffer solution (130 ml) added and stirred at the same temperature. To this reaction mixture above prepared stock solution in lot wise added at 55-60°C and stirred at the same temperature. Distilled off the solvent completely from reaction mixture. To the obtained compound water and ethyl acetate added at 25-30°C. Separated the organic from the mixture and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with water; followed by with aqueous sodium chloride solution. Distilled off solvent completely from organic layer to get the title compound.

Yield: 130.5 g.

Example 7: Preparation of Cenobamate of formula 1

Chloro sulfonyl isocyanate (71.86 g) was added to pre-cooled mixture of (R)-1-(2-chlorophenyl)-2-(1,2,3,4-tetrazol-2-yl)ethan-1-ol (95 g) and tetrahydrofuran (950 ml) at -10 to -15°C temperature and stirred at the same temperature. Water added to the reaction mixture at -15°C, raised the reaction mixture temperature to 25-30°C and ethyl acetate added. Separated the organic from the mixture and the aqueous layers was extracted with ethyl acetate. Combined the organic layers and washed with water, aqueous sodium bicarbonate solution and followed by aqueous sodium chloride solution. Distilled off the solvent completely from organic layer. To the obtained compound ethyl acetate added at 25-30°C and strirred at the same temperature. Filtered the mixture, distilled off the solvent and co-distilled with isopropanol. Isopropanol (171 ml) added to obtained compound at 30°C, heated to 50-55°C and stirred at the same temperature. To the obtained solution, n-heptane (342 ml) added at 50-55°C and stirred at the same temperature. Cooled the reaction mass to 25-30°C and stirred at the same temperature. Filtered the solid, washed with n-heptane and dried to get the title compound.

Yield: 81 g; Purity by HPLC: 99.84% and Chiral purity by HPLC: 100%; PXRD pattern of obtained compound was depicted in figure-1.

Example 8: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. Cooled the solution to 40-45°C and n-heptane (7.2 ml) added. Cooled the mixture to 0-5°C and stirred at the same temperature. Filtered the solid, washed with the mixture of n-heptane and isopropanol and dried to get the title compound.

Yield: 1.67 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 9: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. To this solution, n-heptane (7.2 ml) added and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with the mixture of n-heptane and isopropanol and dried to get the title compound.

Yield: 1.6 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 10: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. Cooled the solution to 10-15°C and stirred at the same temperature. Filtered the solid, washed with isopropanol and dried to get the title compound.

Yield: 1.2 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 11: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. This solution was added to the pre-cooled n-heptane (7.2 ml) at 10-15°C and stirred at the same temperature. Filtered the solid, washed with the mixture of n-heptane and isopropanol and dried to get the title compound.

Yield: 1.65 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 12: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. Cooled the solution to 41-44°C, n-heptane (7.2 ml) added and stirred at the same temperature. Cooled the mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with the mixture of n-heptane and isopropanol and dried to get the title compound.

Yield: 1.7 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 13: Preparation of crystalline Form of Cenobamate

Dissolved Cenobamate (2 g) in isopropanol (3.6 ml) at 50-55°C and stirred at the same temperature. To this solution n-heptane (7.2 ml) added at the same temperature and stirred. Cooled the mixture to 25-30°C and stirred at the same temperature. Filtered the solid, washed with the mixture of n-heptane and isopropanol and dried to get the title compound.

Yield: 1.7 g; PXRD pattern of obtained compound was depicted in figure-1.

Example 14: Preparation of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone [formula 2]

Bromine (144.71g) was added in lot wise to the solution of 1-(2-chlorophenyl)ethanone (100 g) in acetic acid (500 ml) at 20-25°C. The reaction mixture stirred at 25-30°C. Water (1000 ml) and sodium sulfite (138.6 g) were added to reaction mixture at 25-35°C and stirred at the same temperature. Toluene was added to the reaction mixture at 30-35°C and cooled to 0-5°C. Separated the both organic and aqueous layers and aqueous layer is extracted with toluene. Combined the organic layers and washed with water, followed by with aqueous sodium carbonate solution and further with aqueous sodium chloride solution. Solvent was completely distilled off from organic layer to get 2 -bromo -2 –chloroacetophenone**.** To the above obtained compound n-butyl acetate (1450 ml), dimethyl formamide (14 ml), potassium carbonate (102.8 g) and 1H-tetrazole (43.05 g) were added at 25-30°C, heated the reaction mixture to 45-50°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C, filtered and washed with n-butyl acetate. Water added to the obtained filtrate at 25-30°C, separated the both organic and aqueous layers. Organic layer washed with aqueous sodium chloride solution . Distilled off the solvent completely from the organic layer and further co-distilled with methyl tertiary butyl ether. Dissolved the obtained compound in Methyl tertiary butyl ether at 50-55°C. Cooled the solution to 25-30°C and stirred at the same temperature. Removed the precipitated solid by filtration, washed with methyl tertiary butyl ether. Distilled off solvent completely from the filtrate and co-distilled with isopropanol. Dissolved the obtained compound in isopropanol at 60-65°C and cooled the solution to 25-30°C. Water added to the obtained solution at 25-30°C and stirred at the same temperature. Cooled the mixture to 5-15°C and stirred. Filtered the solid, washed with mixture of isopropanol and water and dried to get the title compound.

Yield: 58.0 g. Purity by HPLC: 95.72%, 1N-Ketone impurity: 4.15%.

Example-15: Preparation of Cenobamate for [formula-1]

Preparation of buffer solution: Triethanolamine (67.01 g) is slowly added to mixture of water (760 ml) and magnesium sulfate heptahydrate (0.19 g) at 25-30°C and stirred at the same temperature.

Preparation of stock solution: Mixture of isopropanol (540 ml) and buffer solution (360 ml) stirred at 25-30°C.

Mixture of 1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone (100 g), isopropanol (1100 ml) and buffer solution (300 ml) heated to 52-58°C. The mixture of beta NADP monosodium salt (0.1 g), optimized Ketoreductase Enzyme (1 g) and buffer solution (300 ml) added to the reaction mixture and stirred at the same temperature. During the reaction above prepared stock solution was added in lot wise at 52-58°C. After completion of the reaction, the solvent was distilled off completely from reaction mixture. To the obtained compound water and ethyl acetate added at 25-30°C. Separated the organic layer from the mixture and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Charcoal treatment was given to organic layer and distilled off solvent completely from organic layer to get (R)-1-(2-chlorophenyl)-2-(1,2,3,4-tetrazol-2-yl)ethan-1-ol. Tetrahydrofuran (1000 ml) added to the obtained compound at 25-30°C and cooled to -10 to -20°C. Chlorosulflonylisocyanate (73.13 g) added to reaction mixture at -10 to -20°C and stirred at the same temperature. The reaction mixture was quenched into the pre-cooled water at 0-5°C. Ethyl acetate was added to the mixture. Raised the reaction mixture temperature to 25-30°C. Separated the organic layer from the mixture and the aqueous layers was extracted with ethyl acetate. Combined the organic layers and washed with water, aqueous sodium bicarbonate solution and followed by aqueous sodium chloride solution. Charcoal treatment was given to organic layer. Distilled off the solvent completely from organic layer and co-distilled with isopropanol. Disssolved the obtained compound in isopropanol at 55-60°C. To the obtained solution, n-heptane added at 55-60°C and stirred at the same temperature. Cooled the mixture to 25-35°C and stirred at the same temperature. Filtered the solid, washed with the mixture isopropanol and n-heptane and dried to get the title compound.

Yield: 92.0 g. Purity by HPLC: 99.81%.

Example-16: Preparation of Cenobamate for [formula-1]

1-(2-chlorophenyl)-2-(2H-tetrazol-2-yl)ethanone (100 g) and isopropanol (700 ml) were added to the mixture of water (300 ml), dipotassium hydrogen phosphate (3.74 g), potassium dihydrogen phosphate (1.15 g), wet cell mass (50 g) (having the ketoreductase activity), β-Nicotinamide adenine dinucleotide monosodium salt (NAD) (0.2 g) at 25-30°C, heated the mixture to 55-60°C and stirred at the same temperature. Cooled the reaction mixture to 25-30°C and acidified using aqueous hydrochloric acid solution. Filtered the mixture through hy-flow bed and washed with isopropanol. Distilled off the solvent completely from filtrate. To the obtained compound water and ethyl acetate added at 25-30°C. Separated the organic layer from the mixture and the aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aqueous sodium chloride solution. Charcoal treatment was given to organic layer and distilled off solvent completely from organic layer to get (R)-1-(2-chlorophenyl)-2-(1,2,3,4-tetrazol-2-yl)ethan-1-ol. Tetrahydrofuran (1000 ml) added to the obtained compound at 25-30°C and cooled to -10 to -20°C. Chlorosulflonylisocyanate (73.13 g) added to reaction mixture at -10 to -20°C and stirred at the same temperature. The obtained reaction mixture added to the pre-cooled water at 0-5°C and ethyl acetate added. Raised the reaction mixture temperature to 25-30°C. Separated the organic from the mixture and the aqueous layers was extracted with ethyl acetate. Combined the organic layers and washed with water, aqueous sodium bicarbonate solution and followed by aqueous sodium chloride solution. Charcoal treatment is given to organic layer. Distilled off the solvent completely from organic layer and co-distilled with isopropanol. Isopropanol (180 ml) added to obtained compound at 30°C, heated to 55-60°C and stirred at the same temperature. To the obtained solution, n-heptane (360 ml) added at 55-60°C and stirred at the same temperature. Cooled the reaction mass to 25-30°C and stirred at the same temperature. Filtered the solid, washed with the mixture of isopropanol and n-heptane and dried to get the title compound.

Yield: 81.4 g; Purity by HPLC: 99.92%.

Example-17: Purification of Cenobamate of formula-1

Cenobamate (50 g) dissolved in ethyl acetate (400 ml) at 25-30°C. Filtered the obtained solution, distilled off the solvent from the filtrate and co-distilled with isopropanol. Dissolved the obtained compound in isopropanol at 50-60°C. N-heptane was slowly added to the above solution at 50-60°C and stirred at the same temperature. Cooled the mixture to 20-30°C and stirred at the same

temperature. Filtered the solid, washed with the mixture of isopropanol and n-heptane and dried to get the title compound.

Yield: 44.4 g; Purity by HPLC: 99.97% and Chiral purity by HPLC: other enantiomer Not Detected; PXRD pattern of obtained compound was depicted in figure-1.

Example-18: Preparation of Cenobamate of formula-1

The process described in example-17 is executed in kilo grams level got pure Cenobamate with 91.3% of yield. Cenobamate obtained according to this example having Particle size is D90: 735.5 µm, D50: 264.3 µm and D10: 33.4 µm.

The aforementioned Cenobamate undergoes additional milling, resulting in particle sizes of D[90]: 409.8 µm, D[50]: 126.6 µm, and D[10]: 16.3 µm.

Drawing

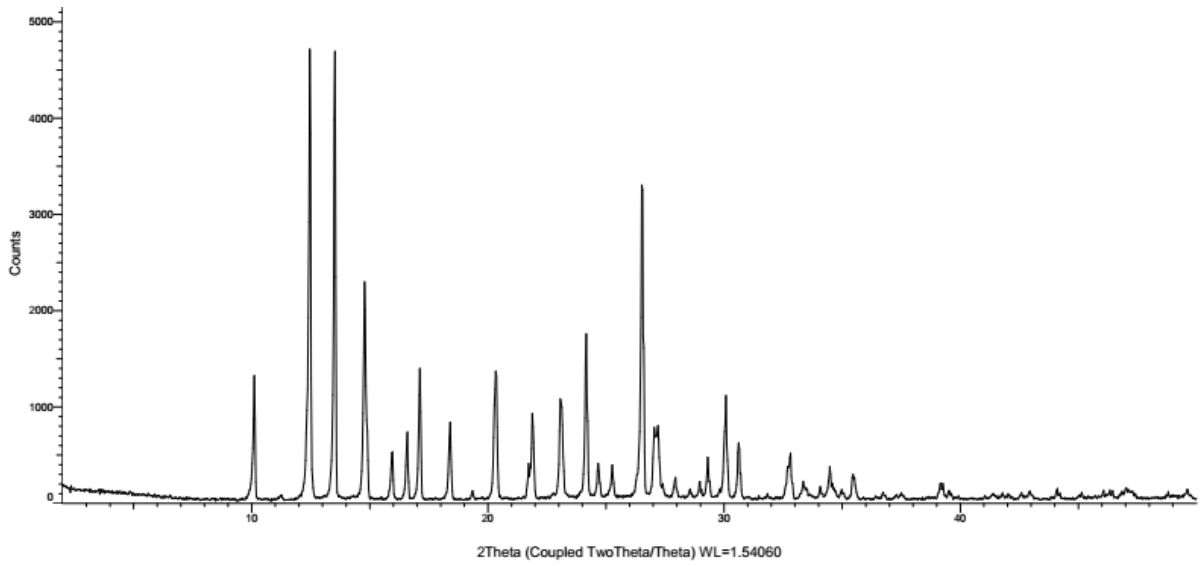


Figure-1

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