Patent Claims

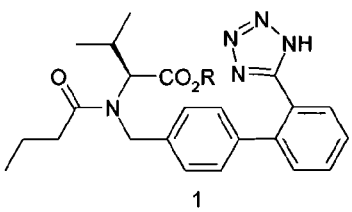
1.A method of synthesizing valsartan, characterised in that said method includes the following steps:

(1) Mixing compound 3 (N-[(2'-cyano-1, 1'-biphenyl-4-yl)alkyl]-L-valine ester hydrochloride) to uniformity with 0.5-10 times the weight of aromatic solvent and carbonate salt aqueous solution; controlling the temperature to 0-30°C and starting the dropwise addition to the mixture of 0.4-0.8 times the weight of pentanoyl chloride with 1-10 times the weight of aromatic solvent; completing the dropwise addition in 0.5-4 hours, and maintaining 10-40°C and mixing for 1-3 hours; separating off the aqueous layer, washing the organic layer with saturated aqueous salt solution, and obtaining a pentanoylated product solution which is directly used for subsequent synthesis or the solvent is partially evaporated to provide a precipitated compound of material 2 (N-(1-pentanoyl)-N-[4-[2-(5-cyano)phenyl]benzyl]-L-valine alkyl ester;

(2) Using the precipitated compound material 2 (N-(1-pentanoyl)-N-[4-[2-(5-cyano)phenyl]benzyl]-L-valine alkyl ester solution of the above preparation step or compound 2 (N-(1-pentanoyl)-N-[4-[2-(5-cyano)phenyl]benzyl]-L-valine alkyl ester solid dissolved in solvent, where the said solvent is the same as or different to the solvent used in step(1);

adding 0.5-4.0 times the pentanoyl product weight of a metal salt of hydrazoic acid and 0.5-2.0 times the weight of amine salt or Lewis acid to this solution;

stirring to uniformity, heating to 70-150°C to react under reflux for 10-50 hours and after the reaction, cooling to room temperature and adding saturated aqueous salt solution for washing, then adding 10% -30% aqueous solution of alkali to the organic layer; controlling the temperature to 0-40°C and reacting for 4-10 hours, then separating off the organic layer, washing the alkali layer by adding a suitable amount of aromatic solvent, reducing the temperature to 0°C or less and adjusting the pH to 1-2 with hydrogen chloride aqueous solution; then extracting using ethyl acetate, washing the organic layer with saturated aqueous salt solution, evaporating off part of the ethyl acetate and cooling to precipitate crystals, and filtering to get compound 1:



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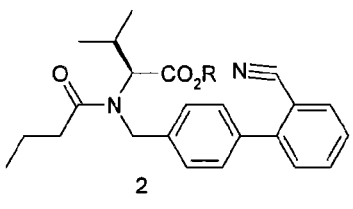

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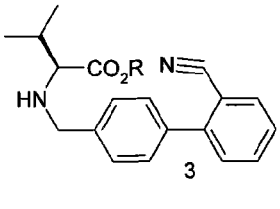

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Compound 1 is N-(1-pentanoyl)-N-[4-[2-(1H-tetrazol-5-yl)phenyl]benzyl]-L-valine, wherein R is hydrogen, methyl, ethyl, isopropyl or benzyl;

when R is H, compound 1 is valsartan;

Compound 2 is N-(1-pentanoyl)-N-[4-[2-(5-cyano)phenyl]benzyl]-L-valine alkyl ester, wherein, the R is hydrogen, methyl, ethyl, isopropyl or benzyl;

Compound 3 is N-[(2'-cyano-1,1-biphenyl-4-yl)alkyl]-L-valine ester hydrochloride, wherein, R is hydrogen, methyl, ethyl, isopropyl or benzyl.

2. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the amine salt of step (2) is triethylamine, methylamine, ethylene diamine or tert.butylamine.

3. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the step (2) Lewis acid is an organic salt of triethylamine salt, methylamine salt, ethylene diamine salt or tert. butylamine salt, or is an inorganic salt of ammonium chloride, zinc chloride or ferrous sulphate; the acid radical of the stated amine salt or Lewis acid is an inorganic acid radical of hydrochloric acid radical, sulphuric acid radical or nitric acid radical or is an organic acid radical of oxalic acid radical, ethane dioic acid radical (sic) or p-toluene sulfonic acid radical.

4. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the hydrazoic acid metal salt of step (2) is sodium azide, potassium azide or lithium azide.

5. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the stated solvent is toluene, p-chlorotoluene or xylene, preferable toluene.

6. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the reaction of step(2) is carried out within a temperature range of 70-150°C.

7. A method of synthesizing valsartan in accordance with Claim 1, characterised in that the compound of formula 1 produced in step (2) can undergo an ester hydrolysis reaction without isolation to obtain valsartan.

8. A method of synthesizing valsartan in accordance with Claim 1, characterised in that said method includes obtaining a compound of formula 2 by reacting a compound of formula 3 and pentanoyl chloride in solvent in the presence of alkali, separating the alkali and the acid type salt, then isolating the compound of formula 2 without having to separate from the solvent, and using directly to prepare the compound of formula 1.

9. Method in accordance with Claim 8, wherein the said solvent is an aromatic hydrocarbon solvent of toluene, p-chlorotoluene or xylene.

10. Method in accordance with Claim 8, wherein the alkali is carbonate salt or hydrogen carbonate salt of an alkali metal or alkaline earth metal, and is potassium carbonate, sodium carbonate, magnesium carbonate, potassium hydrogen carbonate, sodium hydrogen

carbonate or magnesium hydrogen carbonate.

Specification

A method of synthesizing valsartan

Technical field

This invention belongs to the technical field of drugs, more specifically to an improved method of synthesis of valsartan of the kind that does not require the participation of a tin compound in the reaction.

Technological background

Valsartan is a synthetic chemical drug which is effective for the treatment of hypertension, whose chemical name is (S)-N-(1-oxopentyl)-N-[4-[2-(1 H-tetrazol-5-yl)phenyl]benzyl]-L-valine, {English name (S)-N-pentanoyl-N-[[2'-(1 H-tetrazole-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine (valsartan)}. The synthesis method is mainly divided into two parts: the synthesis(including ester protection) of the condensation compound (N-[(2'-cyano-1, 1'-biphenyl-4-yl)alkyl]-L-valine ester)(hydrochloride salt), and the synthesis (including pentanoylation) of valsartan;

The main synthesis routes of the condensation compound are: 1. with 2-cyano-4'-bromomethyl biphenyl as raw material, condensation with carboxy-protected L-valine to obtain the condensation compound, or 2. with 2-cyano-4'-formyl biphenyl as the raw material, condensation and reduction with carboxy-protected L-valine to obtain the condensation compound. The basis of all the syntheses of valsartan is the reaction of the condensation compound and sodium azide as raw materials, under the catalysis of a haloalkyl tin for more than 40 hours. Because of using a tin-containing reagent, the residual tin will carry through directly into the final product, but organic tin compounds are also compounds with very strong toxicity. According to drug ICH demands, organic tin compound should be very strictly controlled to within 1 ppmm in the finished product. Specific references in relevant patent and literature are in US5399578, J.Med.Chem. 1991, Vol.34, No.8, 2525-2547 and the like.

Detailed Description of the Invention

The technical problem that this invention needs to resolve lies in overcoming the weakness of the above-mentioned valsartan synthesis step, getting rid of the participation of the haloalkyl tin compound in the reaction, with a research design of a novel process to improve the synthesis, which will raise the overall yield of valsartan, lower production and material costs, and reduce an environmental pollution.

This invention has provided an improved method of synthesising valsartan, in order to

attain the objective of this invention. This invention takes the condensation compound as raw material, and after a pentanoylation reaction, does not need the participation of a tin compound in the reaction to complete the synthesis of valsartan.

1:N-(1-pentanoyl)-N-[4-[2-(1 H-tetrazol-5-yl)phenyl]benzyl]-L-valine (R is a suitable substituent such as hydrogen, methyl, ethyl, isopropyl or benzyl etc.)

2:N-(1-pentanoyl)-N-[4-[2-(5-cyano)phenyl]benzyl]-L-valine alkyl ester(R is a suitable substituent such as hydrogen, methyl, ethyl, isopropyl or benzyl etc.)

3:N-[(2'-cyano-1, 1'-biphenyl-4-yl)alkyl]-L-valine ester hydrochloride (R is a suitable substituent such as hydrogen, methyl, ethyl, isopropyl or benzyl etc.)

The specific method of this invention is to: (1) mix N-[(2'-cyano-1, 1'-biphenyl-4-yl)alkyl]-L-valine ester (abbreviated as the condensation compound) (hydrochloride) to uniformity with 0.5-10 times the weight of aromatic solvent and carbonate salt aqueous solution; control the temperature to 0-30°C and start the dropwise addition to the mixture of 0.4-0.8 times the weight of pentanoyl chloride with 1-10 times the weight of aromatic solvent, completing the dropwise addition in 0.5-4 hours; maintain 10-40°C and mix for 1-3 hours; and separate off the aqueous layer and wash the organic layer with saturated aqueous salt solution, to obtain a pentanoylated product solution which is directly used for subsequent synthesis or evaporating off part of the solvent to provide a precipitated pentanoylated product solid for use; (2) using the solution of the pentanoylation product of above preparation step or a solution of the pentanoylation product solid dissolved in a solvent which is the same as (or may be different from) the solvent used in step (1), add 0.5-4.0 times the pentanoyl product weight of a metal salt of hydrazoic acid and 0.5-2.0 times the weight of amine salt or Lewis acid to this solution, and stir to uniformity, heat to 70-150°C, react under reflux for 10-50 hours; after the reaction, cool to room temperature and add saturated aqueous salt solution for washing, then add 10% -30% aqueous solution of alkali to the organic layer, control the temperature to 0-40°C and react for 4-10 hours, then separate off the organic layer, add a suitable amount of aromatic solvent to the alkali layer to wash, reduce the temperature to 0°C or less and adjust the pH to 1-2 with hydrogen chloride aqueous solution, then extract using ethyl acetate, wash the organic layer with saturated aqueous salt solution, evaporate off part of the ethyl acetate and cool to precipitate crystals, and filter to obtain valsartan.

In the method of this invention,the alkyl group in the stated condensation compound N-[(2'-cyano-1, 1'-biphenyl-4-yl)alkyl]-alkyl]- L-valine ester is a suitable substituent, such as methyl, ethyl, isopropyl, benzyl or the like, and the aromatic solvent is various acceptable solvents such as toluene, p-bromotoluene, xylene or the like, preferably toluene or p-bromotoluene; the amount of solvent used is 1.5-20 times that of the weight of the condensation compound (hydrochloride salt), preferably 10 times; the carbonate salt is

sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or the like; the metal salts of hydrazoic acid include sodium azide, potchloric acid root, sulphuric acid root, nitric acid root etc. inorganic acid radical and ethane dioic acid root, oxalic acid root, the p-toluene sulfonic acid root organic acid radical,assium azide and the like, the amine salt or other Lewis acid is an organic salt, such as triethylamine salt, methylamine salt, ethylene diamine salt, tert. butylamine salt or the like, or inorganic salt such as ammonium chloride, zinc chloride, ferrous sulphate etc., the acid radical of the amine salt or other Lewis acid is an inorganic acid radical such as the hydrochloric acid radical, sulphuric acid radical, nitric acid radical etc. or an organic acid radical such as ethane dioic acid radical, (sic) oxalic acid radical, p-toluene sulfonic acid radical, most preferably the triethylamine hydrochloride salt. Two steps are involved in this invention, the above-mentioned step (1) which is a pentanoylation and step (2) which is the synthesis of valsartan. The reaction solvent for both steps can be selected from various suitable solvents, such as toluene, p-bromotoluene, xylene and the like, and the solvent chosen for the two steps can be the same or different, but it is preferable to choose the same solvent, most preferably toluene.

The method of this invention gives a high yield, the overall yield calculated from the condensation compound can be more than 75%, and has the following remarkable advantages:

1) Organotin halide, which is expensive and strongly corrosive and has a comparatively large risk of easily damaging the environment, is not used in the improved synthesis of valsartan, and on this basis avoids exceeding the standard for residues of the heavy metal tin in the product.

2) The simple solvent for the two-step reaction is chosen for simple recovery and relatively low price, and can synthesise valsartan by a one-pot method, and it is possible not to switch over the solvent midway, moreover the individual solvents have good promoting action on the reaction, for example using p-bromo toluene to act as the solvent can shorten the reaction time to 10 hours, greatly increasing the work efficiency. This is advantageous for large-scale production.

Example 1

50 L drinking water was added, then 25 kg potassium carbonate was added and stirred until dissolved, then 20 kg condensation compound hydrochloride salt and 150 L toluene were added and stirred until dissolved. The temperature was controlled to 20-30°C and dropwise addition of a liquid mixture of 9 kg pentanoyl chloride and 25 L toluene was started. Dropwise addition was completed in about 2 hours, then the mixture was stirred for an hour while maintaining the temperature at 2 about 30°C to react, and left to stand to separate into layers. The lower, aqueous layer was separated off, and saturated aqueous salt solution was

added to the organic layer for washing. The aqueous salt layer was separated off, and the organic layer (pentanoylated material) was kept for use. Using the pentanoylated material solution prepared in the step above, sodium azide 7.3 Kg and triethylamine hydrochloride salt 17.8 kg were added and stirred to uniformity, and heated under reflux,to react for 20 hours. After refluxing the mixture was cooled to 30°C, then saturated aqueous salt solution 50 L was added, and the mixture was left to stand to separate into layers. The aqueous salt layer was separated off, and the organic layer was washed again using a suitable amount of saturated aqueous salt solution. 13% KOH solution 180 L was added to the organic layer, the temperature was controlled to 40°C and reaction was carried out for 4 hours, and the organic layer was separated off. The alkali layer was washed by adding a suitable amount of toluene and the toluene layer was separated off. The temperature was reduced to 0°C, then 6N hydrochloric acid was added dropwise, to regulate the pH to 1-2. Then extraction was carried out by the addition of ethyl acetate 400 ml and the aqueous layer was separated off. The organic layer was washed by adding saturated aqueous salt solution, and the layers separated. While maintaining the temperature at 40°C, part of the ethyl acetate was evaporated off at reduced pressure, then the mixture was cooled to -5°C or below for 12 hours to precipitate crystals, and filtered and dried to obtain the product valsartan, yield 78%.

Example 2

Apart from using sodium carbonate to replace the potassium carbonate used in Example 1, everything else is the same as in Example 1, the yield is 75%.

Example 3

Apart from using sodium hydrogen carbonate to replace the potassium carbonate used in Example 1, everything else is the same as in Example 1.

Example 4

Apart from using potassium hydrogen carbonate to replace the potassium carbonate used in Example 1, everything else is the same as in Example 1.

Example 5

Apart from changing the toluene as the aromatic solvent in Example 1 to p-chlorotoluene, everything else is the same as in Example 1.

Example 6

Apart from changing the toluene as the aromatic solvent in Example 1 to xylene, everything else is the same as in Example 1.

Example 7

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 1.

Example 8

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 1.

Example 9

Apart from changing the triethylamine hydrochloride to triethylamine sulfate, everything else is the same as in Example 1.

Example 10

Apart from changing the triethylamine hydrochloride to ethylene diamine hydrochloride, everything else is the same as in Example 1.

Example 11

Apart from changing the triethylamine hydrochloride to tert. butylamine hydrochloride, everything else is the same as in Example 1.

Example 12

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 1.

Example 13

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 1.

Example 14

Apart from changing the toluene as aromatic solvent in Example 2 to p-chlorotoluene, everything else is the same as in Example 2.

Example 15

Apart from changing the toluene as aromatic solvent in Example 2 to xylene, everything else is the same as in Example 2.

Example 16

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 2.

Example 17

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 2.

Example 18

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 2.

Example 19

Apart from changing the toluene as aromatic solvent in Example 3 to p-bromo toluene, everything else is the same as in Example 3.

Example 20

Apart from changing the toluene as aromatic solvent in Example 3 to xylene, everything else is the same as in Example 3.

Example 21

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 3.

Example 22

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 3.

Example 23

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 3.

Example 24

Apart from changing the toluene as aromatic solvent in Example 4 to p-bromo toluene, everything else is the same as in Example 4.

Example 25

Apart from changing the toluene as aromatic solvent in Example 4 to xylene, everything else is the same as in Example 4.

Example 26

Except for changing the sodium azide to potassium azide, everything else is the same as in

Example 4.

Example 27

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 4.

Example 28

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 4.

Example 29

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 4.

Example 30

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 5.

Example 31

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 5.

Example 32

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 5.

Example 33

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 5.

Example 34

Apart from changing the triethylamine hydrochloride to ferrous chloride, everything else is the same as in Example 5.

Example 35

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 6.

Example 36

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 6.

Example 37

Apart from changing the triethylamine hydrochloride to triethylamine sulphate, everything else is the same as in Example 6.

Example 38

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 6.

Example 39

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 6.

Example 40

Apart from changing the triethylamine hydrochloride to ferrous chloride, everything else is the same as in Example 6.

Example 41

Apart from changing the triethylamine hydrochloride to ammonium chloride, everything else is the same as in Example 7.

Example 42

Apart from changing the triethylamine hydrochloride to zinc chloride, everything else is the same as in Example 7.

Example 43

Apart from changing the triethylamine hydrochloride to ferrous chloride, everything else is the same as in Example 7.

Example 44

Except for changing the sodium azide to potassium azide, everything else is the same as in Example 37.

Example 45

Except for changing the sodium azide to lithium azide, everything else is the same as in Example 37.

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