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(71) Applicant and
(72) Inventor: **POTLURI, Ramesh, Babu** [IN/IN]; #417, 4th Floor, Nilgiri, Aditya, Enclave, Ameerpet, Hyderabad 500 038 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **VENKATA SUBRAMANIAN, Hariharakrishnan** [IN/IN]; #417, 4th Floor, Nilgiri, Aditya, Enclave, Ameerpet, Hyderabad 500 038 (IN). **KODALI, Hari, Prasad** [IN/IN]; #417, 4th Floor, Nilgiri, Aditya, Enclave, Ameerpet, Hyderabad 500 038 (IN).

(74) Agent: **VISHWANATH, Ramesh, Babu**; Vishwanath & Company, Advocates & Attorneys for Patents & Trademarks, #48 SRT, 1st Floor, Prakash Nagar, Begumpet, Hyderabad 500 016 (IN).

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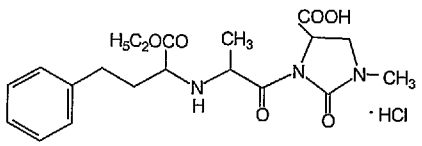
(54) **Title:** PROCESS FOR INDUSTRIALLY VIABLE PREPARATION OF IMIDAPRIL HYDROCHLORIDE



(I)

(57) **Abstract:** The invention relates to a novel method for the preparation of imidapril hydrochloride of formula-I by reacting esters of 4(S)-1-methyl-2-oxoimidazolidine-4-carboxylate of formula-II with (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate of formula-III and hydrolyzing the coupled product with an alcoholic hydrochloride.

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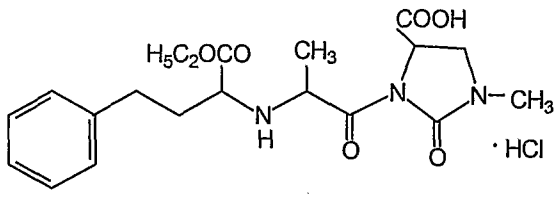
TITLE:

PROCESS FOR INDUSTRIALLY VIABLE PREPARATION OF IMIDAPRIL HYDROCHLORIDE

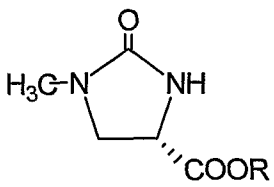
FILED OF THE INVENTION:

The invention relates to a novel method for the preparation of imidapril hydrochloride of formula I

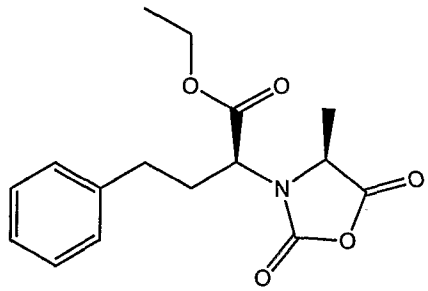


Formula-I

by reacting the compound of formula II with a compound for formula-III followed by reduction/hydrolysis and salting



Formula-II



Formula-III

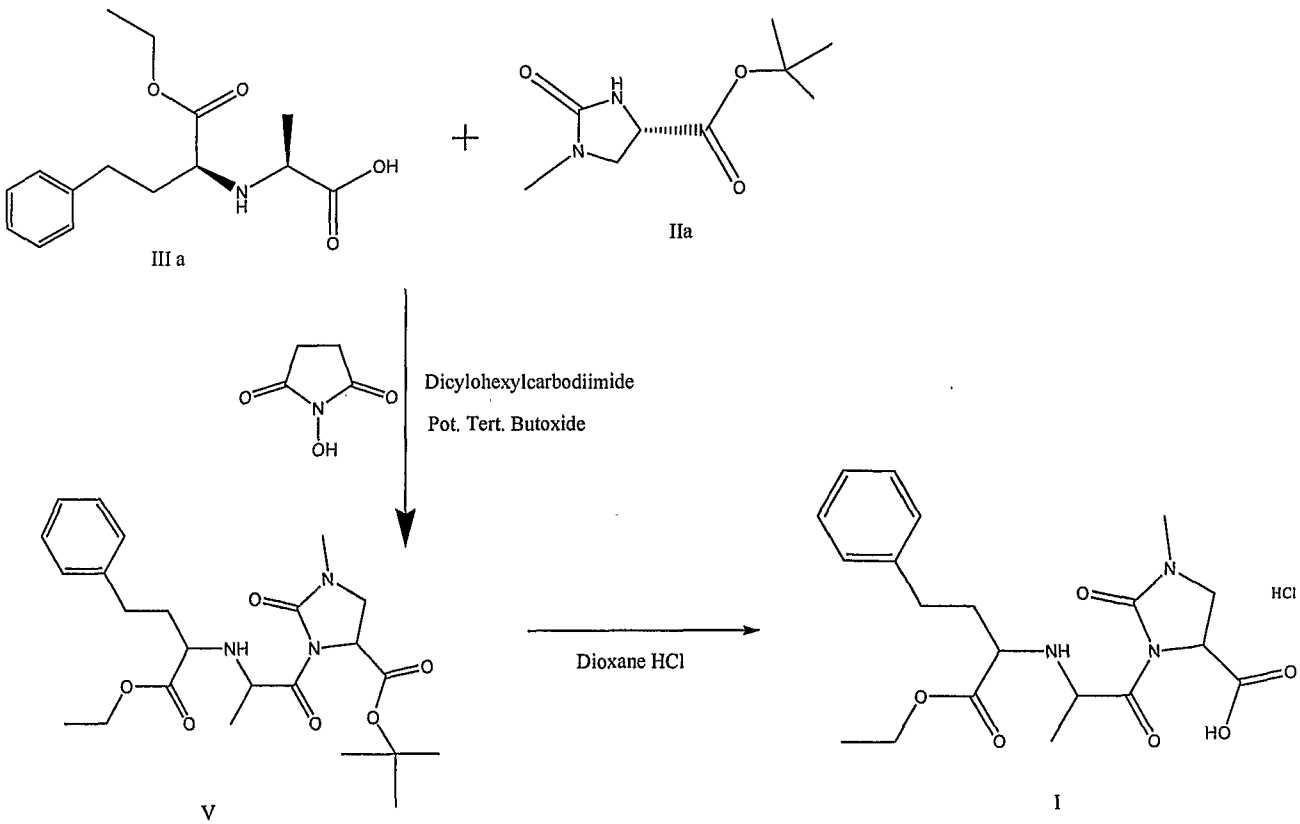
BACKGROUND OF THE INVENTION AND RELEVANT PRIOR ART:

As known in the art, the chemical entity (4S)-3-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3–phenylpropyl]amino]-1–oxopropyl]-1–methyl–2–oxo–4–imidazolidinecarboxylic acid hydrochloride of formula I, known generically as imidapril hydrochloride, belongs to a group of medicines called ACE inhibitors, which block the action of a chemical in the body called angiotensin converting enzyme (ACE). Normally ACE produces another chemical, angiotensin II. Thus imidapril reduces the amount of angiotensin II in the blood.

Angiotensin II has two actions. Firstly it acts on blood vessels to make them narrow and secondly it acts on the kidney to produce less urine. As imidapril stops the production of angiotensin II, these actions are reversed. Therefore more urine is produced by the kidneys, which results in less fluid in the blood vessels. The blood vessels also widen. The overall effect of this is a drop in blood pressure and a decrease in the workload of the heart.

The preparation of a compound of formula I can be achieved by any of the well know methods described in a few patents and publications viz., EP 95163,/US4508727 and JMC **32**,289 (1989).

EP 95163/US4508727 discloses synthesis of imidapril hydrochloride of formula I, employing several stages. This is shown in the following schemes IA and IB

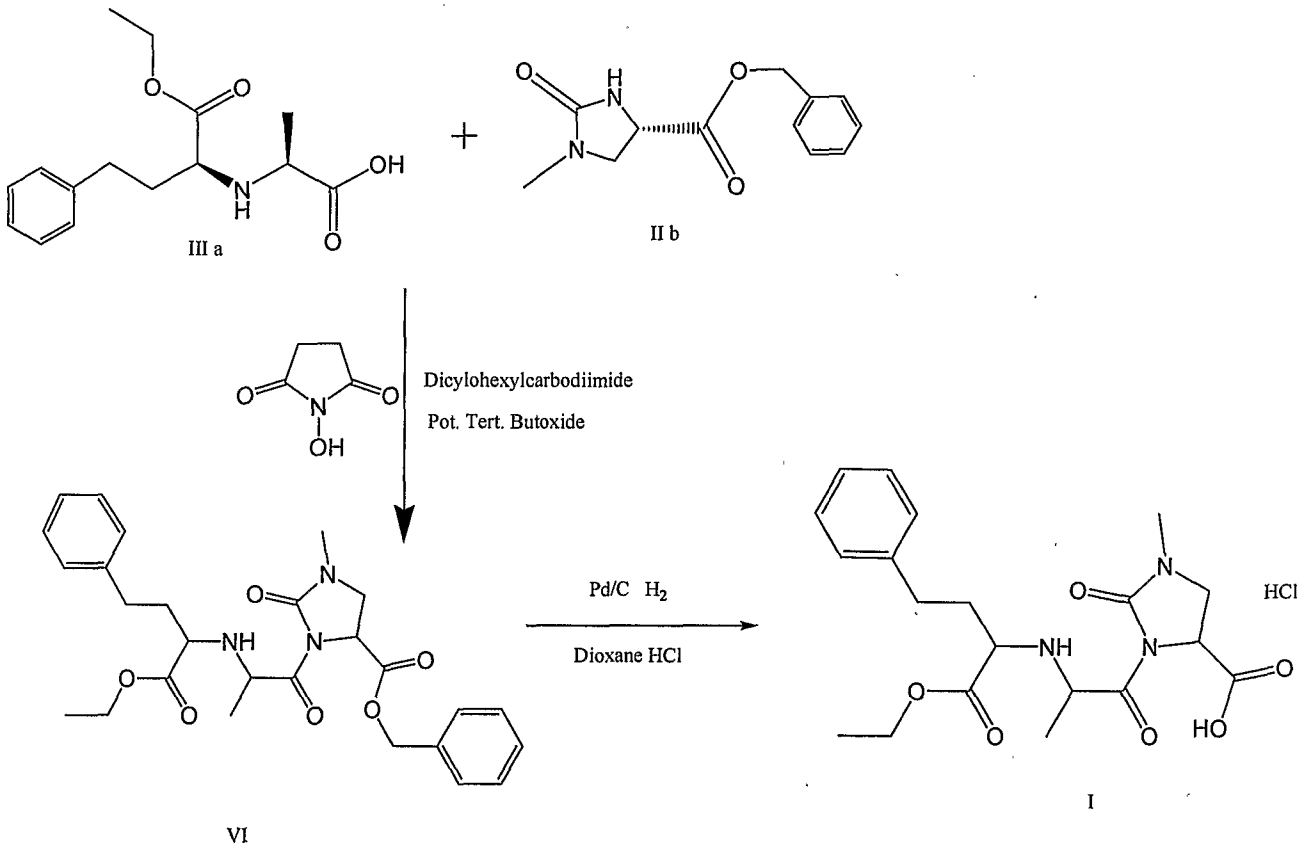


Scheme-I A

As per the scheme IA, ECPP alanine of formula-IIIa is activated with N-hyroxysuccinicimide using dicyclohexylcarbodiimide and the activated ester is coupled with t-butyl imidaozlinone-4-carboxylate of formula-II a in the presence of potassium tert.

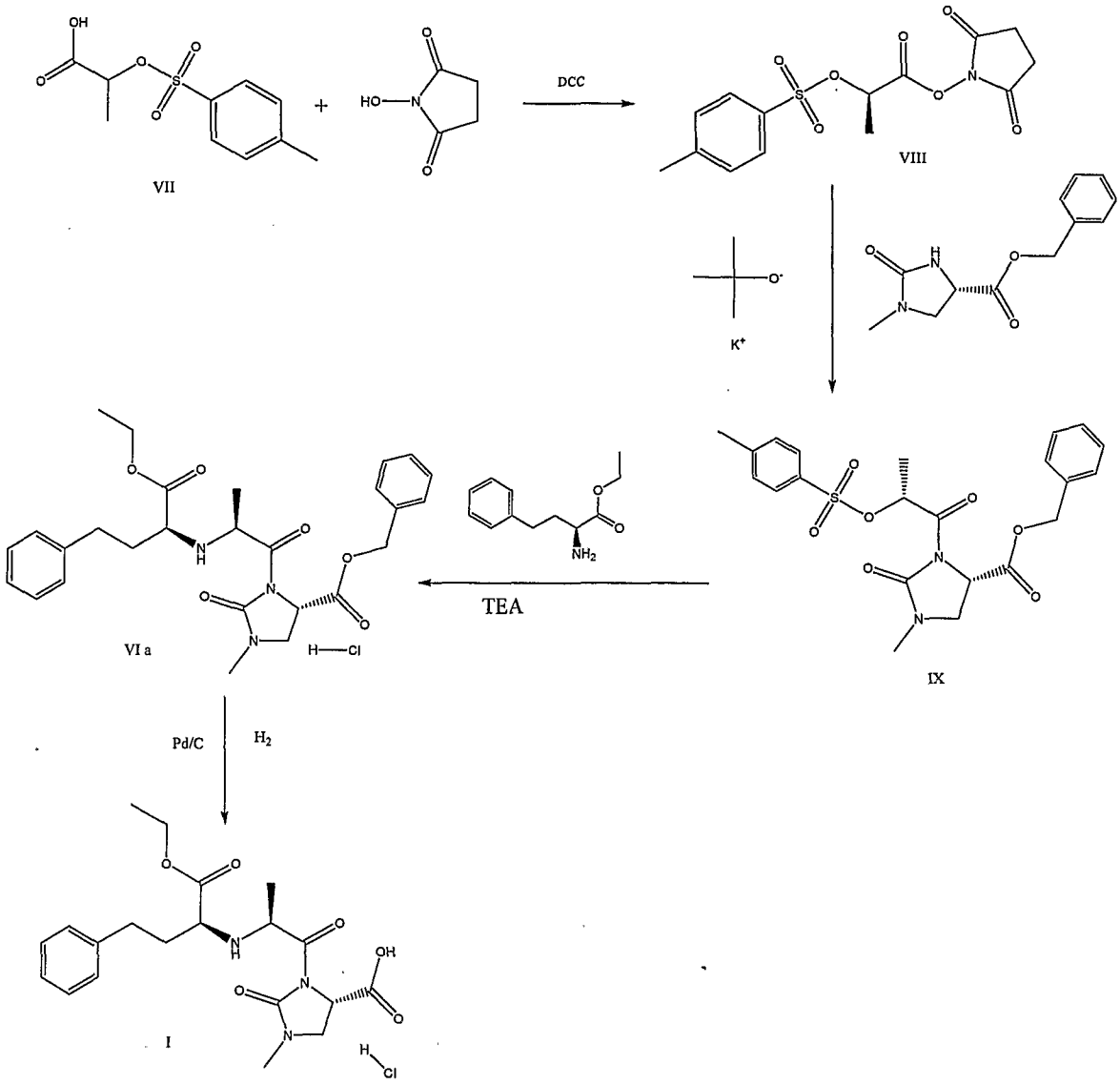
butoxide to give a dipeptide of formula-V, which is converted to the product of formula-I by treatment with dioxane-HCl

The scheme I B describes a methodology, which is similar to the one described in scheme IA, except the fact that benzyl imidazolidinone-4-carboxylate of formula-II b is used instead of the t-butyl ester IIa. The coupled product of formula-VI is debenzylated using Pd/C – H_2 and treated with dioxane-HCl to get the product of formula-I. These data are published in JMC **32,** 289 (1989).



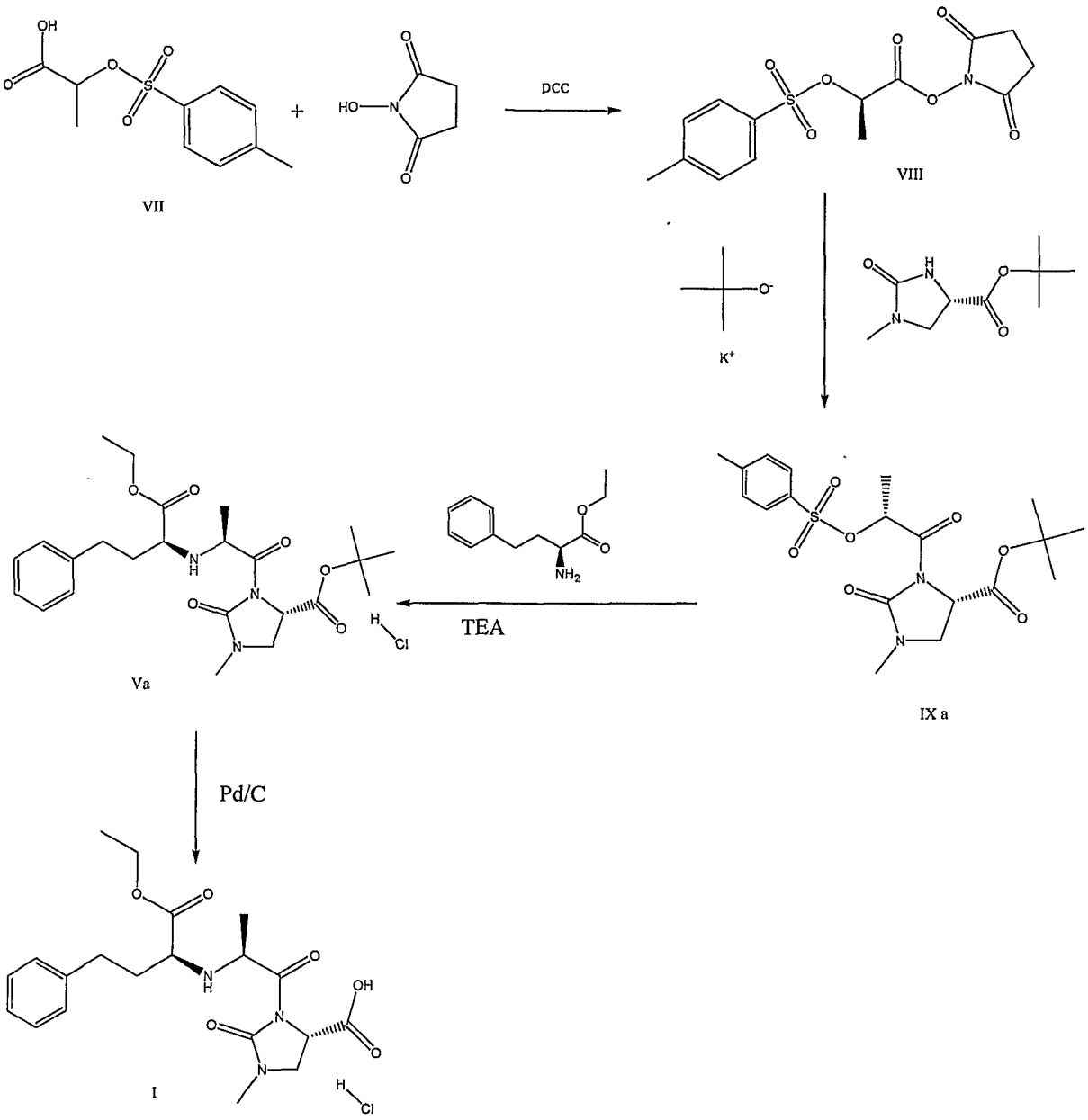
Scheme-I B

The methodology adopted in US patent 5013845 is depicted in scheme II A and II B. As per the scheme IIA 2-(tosyloxy)-propionic acid of formula VII is activated by reacting with N-hyroxysuccinicimide to get a product of formula-VIII, which is coupled with benzyl imidazolidinone-4-carboxylate of formula-II b to give a product of formula-IX. This is reacted with ethyl-(S)-2-amino-4-phenyl butyrate to get a product of formula-VI a. The product of formula-VI a is debenzylated to get imidapril hydrochloride.



Scheme-IIA

A similar sequence of reactions is followed in scheme IIB, where t-butyl imidazolidinone-4-carboxylate of formula-II a is used. Here the tosyloxy derivative of formula IX a is coupled with ethyl-(S)-2-amino-4-phenyl butyrate of formula to get a protected dipeptide of formula V a , which on treatment with dioxane-HCl give imidapril hydrochloride of formula-I



Scheme-IIB

Analyzing the sequence of reactions described in US patent 4508727 (scheme IA and IB) and the results, it can be observed that there are three draw backs viz.,

a) the activation of ECPP alanine using N-hyroxysuccinicimide in presence of dicyclohexylcarbodiimide is tedious process
b) final yields are moderate and
c) moderate yields and use of expensive reagents makes the process uneconomical

Coming to the methodology used as per US patent 5013845 (schemes IIA and IIB), this involves preparation of tosyloxy derivative (VII), followed by activation using N-hyroxysuccinicimide using dicyclohexylcarbodiimide, further coupling and deprotection. Finally a column purification is also involved. This makes the process very tedious and uneconomical.

SUMMARY OF THE INVENTION:

The present invention provides a novel process for the preparation of imidapril of formula I

by reacting esters of 4(S)-1–methyl–2–oxoimidazolidine-4-carboxylate of formula-II with (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate of formula-III in presence of a base like sodium hydride/sodium methoxide, potassium tert. butoxide etc. After the coupling, the protecting group was removed by means of catalytic hydrogenation or hydrolysis to get the required compound

The above description briefly outlines the preferred embodiments of the present invention, which enables those skilled in the art to understand the detailed description that follows. Additional features of the invention will be described hereinafter that form the subject of claims of the invention. Those skilled in the art should appreciate that they can readily use the disclosed concept and specific embodiment as a basis for preparation of similar derivatives. Those skilled in the art should realize such equivalent concept do not depart from the spirit and scope of the invention in its broadest sense.

OBJECTIVES AND ADVANTAGES OF THE INVENTION:

Considering the short comings of the processes described in the prior art, there is every need to develop a method for the synthesis of imidapril by a novel process, which is economical and eco-friendly.

The following are the advantages gained by this invention

a) avoiding costly reagents like dicyclohexylcarbodiimide, N-hydroxysuccinicimide etc.,
b) improving yield to get high quality product.

By achieving these objects, a new economical process giving rise to a quality product will result.

DETAILED DESCRIPTION OF THE INVENTION:

The initial studies for the synthesis involved coupling of ECPP alninoyl chloride hydrochloride with imidazolidinone-4-carboxylate ester using silylated reagent like HMDS and bis silyl acetamide. The reaction was also tried using an organic base. Eventhough product was formed, yields were moderate and impurities were formed. Later attempts were made to synthesise imidapril using the ECPP alanine anhydride viz., (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate of formula-III

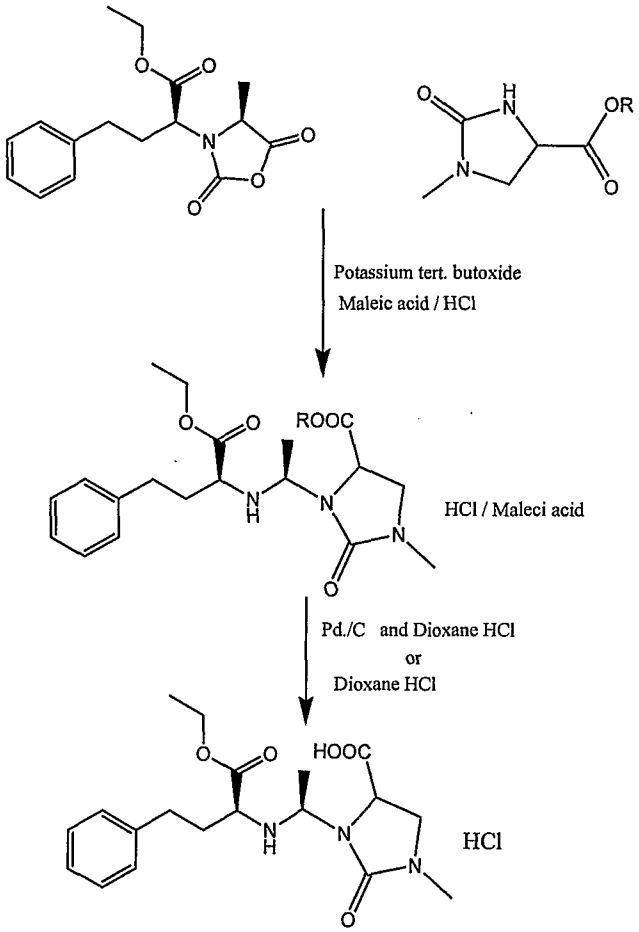
The reaction of the product of formula-III with imidazolidinone-4-carboxylicacid of formula-II was tried using different bases viz., NaH, $NaOBu^t$, $KOBu^t$, $NaNH_2$ etc. It was preferable to use NaH, $Na/KOBu^t$. It was more preferable to use $Na/KOBu^t$. The reaction was studied in different solvents like dichloroethane, dichloromethane, acetonitrile, tetrahydrofuran, 2 or 3 methyl tetrahydrofuran, 1,4-dioxane, dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone, dimethylsulfoxide, sulfolane etc. It was preferable to use solvents like THF, DMF, DMAc, DMSO or sulfolane. It was preferable to conduct the reaction at -100°C to +10 °C. It was more preferable to conduct the reaction at -80 °C to 0 °C. It was still more preferable to conduct the reaction at -65 °C to -10 °C. The progress of the reaction was monitored by TLC and on completion was isolated in the form of maleate or hydrochloride salt. The salt, thus obtained, was neutralized and deprotected to get imidapril hydrochloride of formula-I

The yields at coupling stage and further are very good (overall yield: 82 %) and the product of formula-I is obtained in excellent purity (>99.8%)

Thus the objectives of synthesizing imidapril hydrochloride of formula-I of high purity by an economical process has been achieved by the above deserted process

The starting material viz, esters of 4(S)-1–methyl–2–oxoimidazolidine-4-carboxylate of formula-II with (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate of formula-III can be prepared conventionally by well known methods.

The following scheme was described the invention



EXAMPLE

In the following example, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, this does not limit the scope of the present invention in any way.

I - Preparation of t-butyl-(4S)-3-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-4-imidazolidinecarboxylate hydrochloride

150gms of t-butyl 4(S)-1–methyl–2–oxoimidazolidine-4-carboxylate charged into 450ml of tetrahydrofuran and cooled a temperature of -45 to -50°C. 235gms of (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate was dissolved in 550ml of tetrahydrofuran and added to above reaction mixture at -45 to -50°C. The reaction mass was stirred for 90min at -45 to -50°C and quenched into another flask which contains 1.2lts of ethyl acetate and 600ml of water. The organic layer, after separation, was washed with saturated sodium chloride and dried over anhydrous sodiumsulphate. 350ml of 10% isopropanolic hydrochloride added to the organic layer and concentrated under reduced pressure. After complete removal of the solvent, 600ml of diisopropylether was added. The precipitated crystals were filtered and dried. The product obtained was 338gms with a specific rotation of -57.4°. (The product was characterized by ^{1}H NMR)

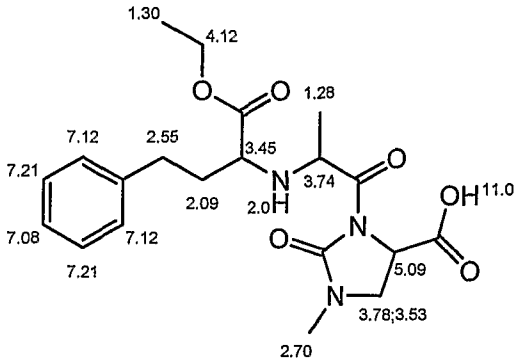
1.28 (3H, -CH_3); 1.30 (3H, -CH_3); 1.40 (9H, 3 x -CH_3); 2.70 (3H;-CH_3); 2.09(2H, -CH_2) ; 2.55 (2H, -CH_2);3.64 (2H, -CH_2); 4.12 (2H, -CH_2); 3.45 (1H,-CH); 3.74 (1H,-CH); 5.05 (1H, -CH); 7.08-7.21 (5H, aromatic CH);2.00 (1H, NH)

II – Preparation of imidapril hydrochloride

300gms of t-butyl-(4S)-3-[(2S)-2-[[(1S)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1-methyl-2-oxo-4-imidazolidinecarboxylate hydrochloride was charged into a flask which contains 1.5lts of dichloromethane and 2.0lts of demineralised water. Reaction mixture pH was adjusted to 10 using aqueous potassium carbonate solution and organic layer was separated. The organic layer washed twice with 500ml each brine solution and dried over sodium sulphate. After complete removal of the solvent under reduced pressure, 750ml of 15% isopropanolic HCl was added and stirred for 6 hours at 25-30°C. 900ml of diisopropylether was added after cooling the reaction mass to 10-15 °C. The precipitated crystals were filtered and dried. The product obtained was 244 gms with a specific rotation of -64.2°, melting point 215-217 °C and purity by HPLC was 99.82%. (The product was characterized by ^{1}H NMR)

Node	Shift	Base	Comment
CH	5.09	1.50	methine
CH2	3.78;3.53	1.37	methylene
OH	11.0	11.00	carboxylic acid
CH3	2.70	0.86	methyl
CH	3.74	1.50	methine

CH3	1.28	0.86	methyl
NH	2.0	2.00	amine
CH	3.45	1.50	methine
CH2	2.09	1.37	methylene
CH2	2.55	1.37	methylene
CH	7.12	7.26	1-benzene
CH	7.21	7.26	1-benzene
CH	7.08	7.26	1-benzene
CH	7.12	7.26	1-benzene
CH	7.21	7.26	1-benzene
CH2	4.12	1.37	methylene
CH3	1.30	0.86	methyl



CLAIMS:

01. An industrially viable process for the preparation of imidapril hydrochloride by
    a) reacting esters of 4(S)-1–methyl–2–oxoimidazolidine-4-carboxylate of formula-II with (S)-ethyl-2-[(S)-4-methyl-2,5-dioxooxazolidin-3-yl]-4-phenylbutanoate of formula-III,
    b) precipitating the coupled (peptide coupling) product as salt of formula-IV,
    c) hydrolyzing with an alcoholic solvent by in-situ conversion of the product of formula IV to the hydrochloride salt of formula I or de-benzylating using a catalyst and hydrogen and converting to the hydrochloride salt of formula-I
02. A claim, as claimed in claim 1a, wherein the reaction of the product of formula-II with the product of formula-II is carried out using a base.
03. A claim, as claimed in claim 2, wherein the base used to activate the ester is of alkali earth oxide such as potassium tertiary butoxide, sodium methoxide / ethoxide
04. A claim, as claimed in claim 1b, wherein the product is isolated as salt of an organic acid or inorganic acid
05. A claim, as claimed in claim 4, wherein, the organic salts are of oxalic acid, maleic acid, fumaric acid, tartaric acid and inorganic acid salts are of hydrochloric acid, hydrobromic acid and sulpuric acid .
06. A claim, as claimed in claim 1c, wherein the hydrolysis of the product of formula-IV carried out using alcoholic hydrochloride
07. A claim, as claimed in claim 1c, wherein debenzylation is carried out using Pd/C and hydrogen and the product obtained is converted to the product of formula I by treatment with alcoholic hydrogen chloride

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2006/000183

A. CLASSIFICATION OF SUBJECT MATTER
IPC[8]: ***C07D 233/38*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[8]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS-databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6541635 B1 (TIEN et al.) 1 April 2003 (01.04.2003) *the whole document* ---	1-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 August 2006 (31.08.2006)	25 September 2006 (25.09.2006)

Name and mailing address of the ISA/ AT	Authorized officer
Austrian Patent Office Dresdner Straße 87, A-1200 Vienna	SLABY S.
Facsimile No. +43 / 1 / 534 24 / 535	Telephone No. +43 / 1 / 534 24 / 348

Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1 (partly), 3 (partly) and 7 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 1 refers to a product of formula IV, which is not defined in the application. According to the example I it seams to be an ester of imidapril hydrochloride. The search had therefore to be restricted to ester of imidapril hydrochloride for the compound of formula IV.
The expression "de-benzylation" in claim 1 and 7 is not clear, as there is no mention of "de-benzylation" in the description. This part of claim 1 and claim 7 have not been searched.
The expression "alkali earth oxide" in claim 3 is not a technical term and does not make sufficiently clear which specific compounds are meant. The search had therefore to be restricted to the compounds explicitly mentioned in the application.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2006/000183

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US B1 6541635	2003-04-01	none	