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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF LOSARTAN

(57) Abstract: The invention relates to an improved process for the preparation of Losartan. Which comprises reacting 2-n-butyl-4-chloro-5-formyl imidazole with 2-(4-bromomethyl) benzonitrile in the presence of a phase transfer catalyst and alkali, and reducing resulting cyano aldehyde to get cyano alcohol which is further reacted with sodium azide in N-methyl pyrrolidinone and a salt to produce Losartan .

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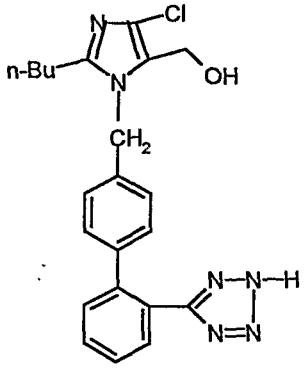
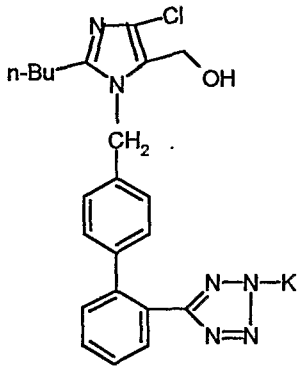
AN IMPROVED PROCESS FOR THE PREPARATION OF LOSARTAN

The invention disclosed in this application relates to an improved process for the preparation of Losartan . Losartan and its potassium salt, having the formulae (1) &(2) respectively are angiotensin - II receptor (Type ATI) antagonists.



LOSARTAN

1



LOSARTAN POTASSIUM

2

In adults Losartan is currently indicated for the treatment of hypertension. (in hypertensive patients with left ventricular hypertrophy, it is also indicated to reduce the risk of stroke).

Background:

Losartan Potassium having the formula **(2)** and its principle active metabolite block the vasoconstrictor and aldosterone. Secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the ATI receptor found in many tissues (e.g., vasicular smooth muscle, adrenal gland) otherwise called as angitensin receptor blockers (ARBs).

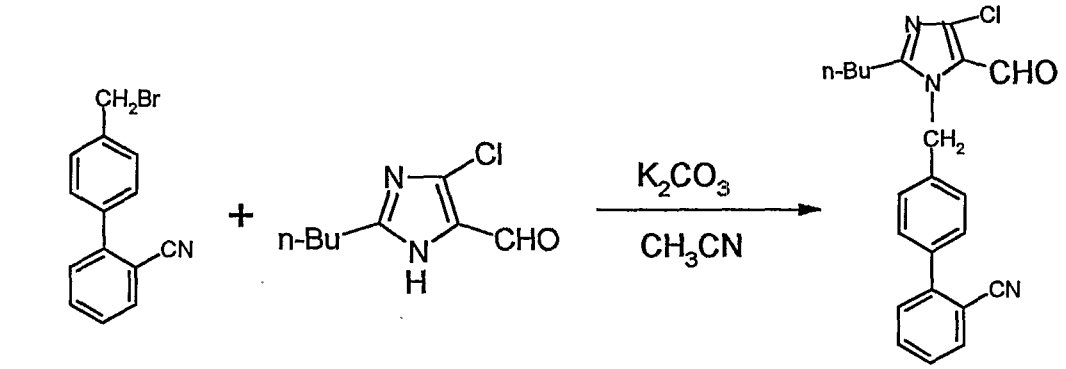
Prior Art

There are many processes recorded in literature. The latest prior art information for the preparation of Losartan is the disclosure made in the patent application of Novartis in their PCT WO 2005/014602 dated 17 Feb 2005.

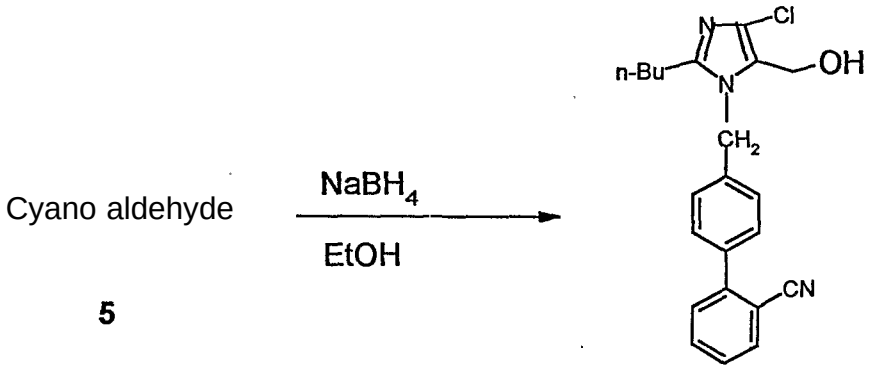
The process described in the application comprises the reaction of 4'-(Bromomethyl)-2-cyanobiphenyl (Bromo OTBN) of the formula (3) with 2-n-butyl-4-chloro-5-formyl

imidazole (BCFI) of ihe formula (4)in the presence of Potassium carbonate and acetonitrile to give cyano aldehyde of the formula (5) . The Cyano aldehyde of the formula (5) is reduced with sodium borohydride to get cyano alcohol of the formula (6). The Cyano alcohol is reacted with diethyl aluminium azide in the presence of triethyl aluminium to give Losartan of the formula (1) .

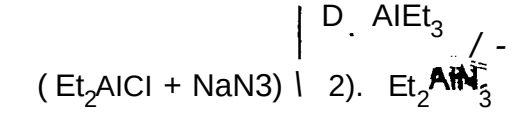
The reaction scheme of the process is shown in the Scheme 1



Bromo OTBN 3 BCFI 4 Cyano aldehyde 5



Cyano alcohol 6



Losartan 1

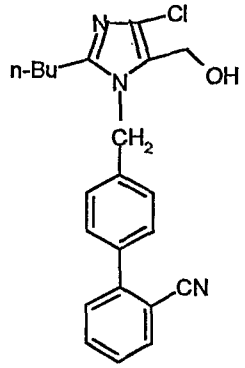
Scheme 1

Even though the process is simple, handling of triemyl aluminium used needs special attention like very anhydrous conditions, reaction* are to be performed under nitrogen or argon and transferring of triethyl aluminium from the containers needs anhydrous

systems. The neat liquid and dense solutions of triethyl aluminium are known to ignite very easily at room temperature in presence of air. (Pyrophoric). So handling of both triethyl aluminium and diethyl aluminium needs special attention like anhydrous conditions, nitrogen atmosphere etc.,

In EP 0578125Al of Takeda Chemical Industries dated 12 Jan 1994, yet another method for the preparation of Losartan has been disclosed in which Trioctadecyl or Trioctyl tin azide has been used as a tetrazole-forming agent. This method also uses the Cyano alcohol of the formula (6). The process comprises reacting the cyano alcohol of the formula (6) with tri-n-octyl tin azide in presence of toluene to give tri-n-octyl tetrazole derivative which was treated with nitrous acid to give Losartan of the formula (1) in 94.7% yield.

The reaction scheme of the process is shown in the Scheme 2



Cyano alcohol 6

1). tri-n-octyl tinazide

Toluene, 120^{0}C, DMF

2). $NaNO_2$ / HCl , yield: 94.7%

Losartan 1

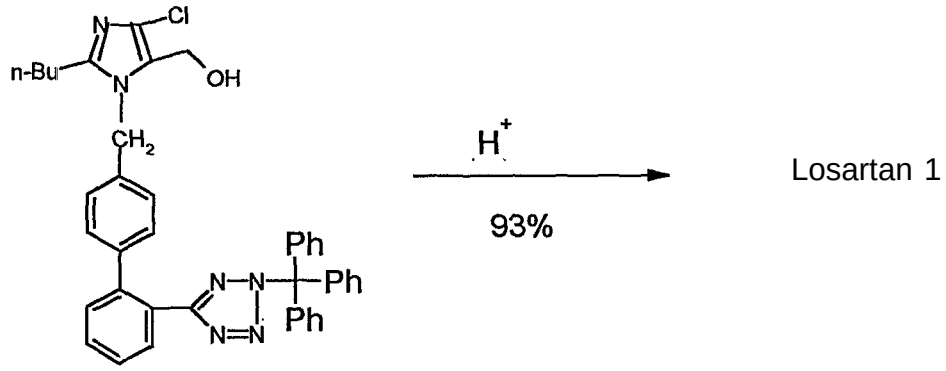
Scheme - 2

Even though the yields are better (94.7%) in this process again handling of tri-n-octyl tin azide is involved and tin (as heavy metal) contaminants in the drug has to be monitored as per pharmacopoeial methods.

Dupont / Merck in their patents and papers always described that trityl losartan of the formula (7) is detritylated to get Losartan.They have used trimethyl tin azide or tri alkyl tin azides for the preparation of tetrazoles. The trityl Losartan of the formula (7) is reacted with mineral acid to give Losartan of the formula (1). The trityl Losartan of the

formula (7) is prepared using trimethyl or trialkyl tin azide for the formation of tetrazole nucleus.

The reaction scheme of the process is shown in the **Scheme 3**

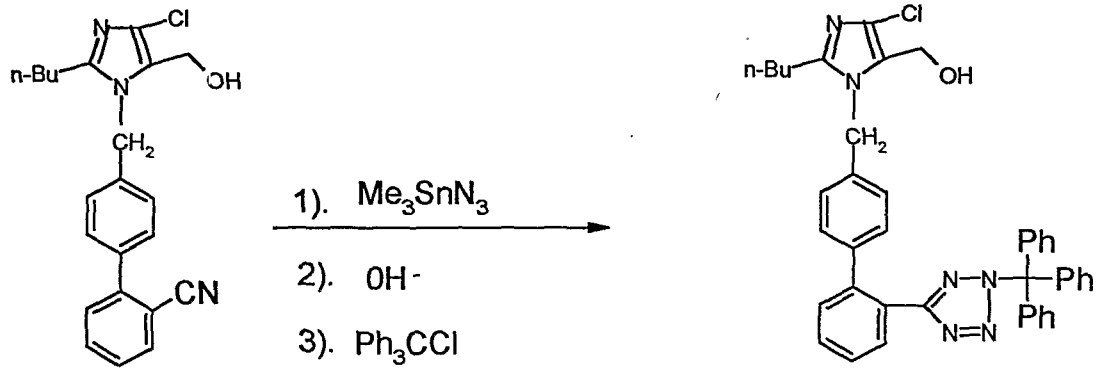


7

Scheme - 3

For example they described in J. Med. Chem 1991, 34, 2525 - 2547, the preparation of compound of the formula 7 as follows.

The Cyano alcohol of the formula (6) was reacted with trimethyl tin azide to give trimethyl tin tetrazole compound, which was hydrolysed to give tetrazole compound. The tetrazole compound was reacted with trityl chloride to give trityl Losartan of the formula (7). The reaction scheme of the process is shown in the **Scheme 4.**



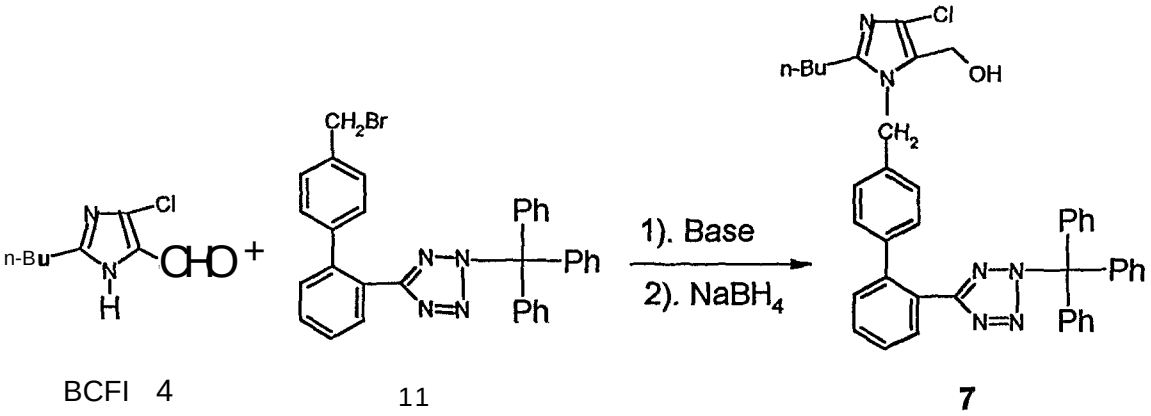
6 7

Scheme 4

In the same paper the compound of the formula (7) is prepared by reacting 2-butyl-4-chloro-5-formyl imidazole of the formula (4) with N-(Triphenylrnethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole of the formula (11) in the presence of base and the

resulting aldehyde is reduced with Sodium borohydride to give Trityl Losartan of the formula (7).

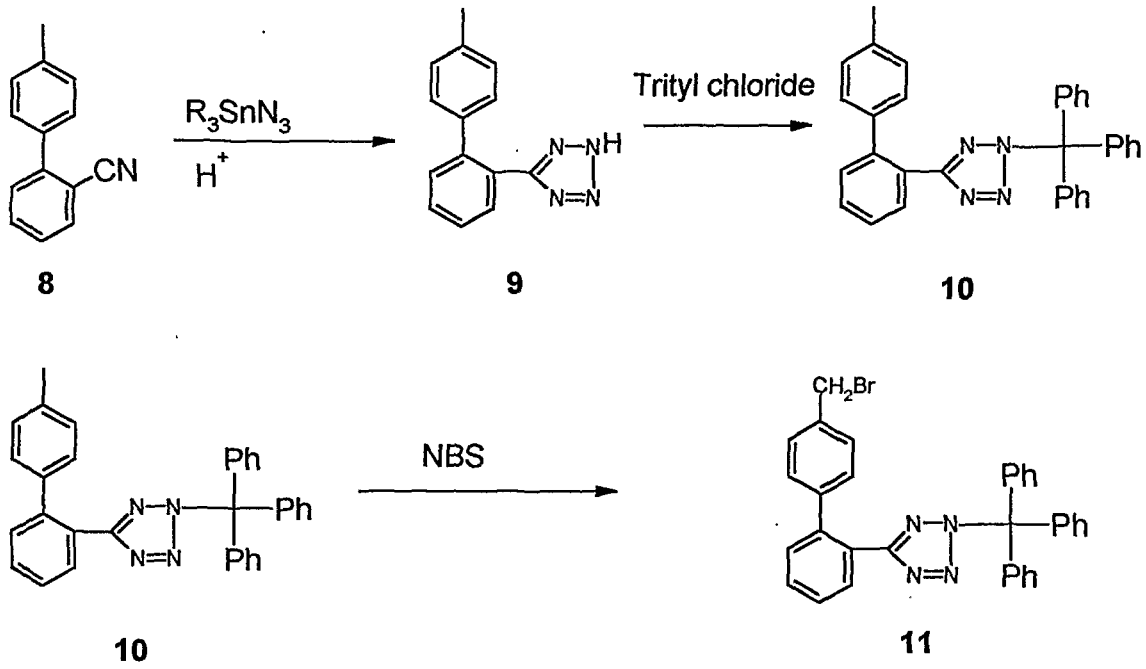
The reaction scheme of the process is shown in **Scheme 5.**



BCFI 4 11 **7**

Scheme 5

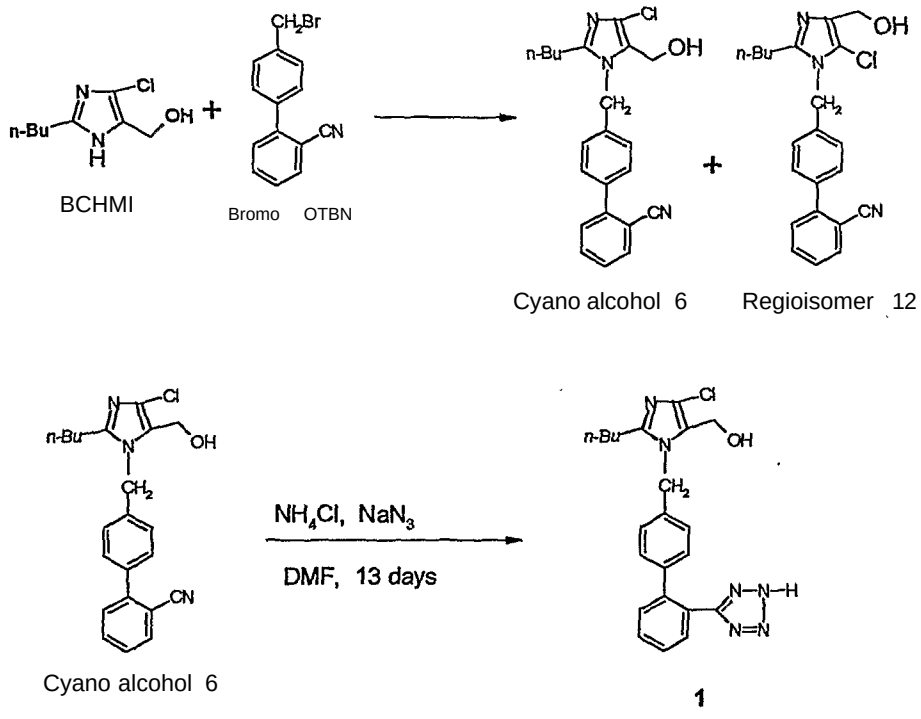
The compound of the formula **(11)** is prepared using tri alkyl tin azide. Ortho tolyl benzonitrile (OTBN of the formula (8) is reacted with trialkyl tin azide followed by hydrolysis to give tetrazole derivative of the formula (9). The tetrazole derivative is reacted with trityl chloride to give trityl tetrazole derivative of the formula (10), which on radical bromination gives compound of the formula **(11).** The reaction sequence is given in the **Scheme 6.**



Scheme 6

Merck / Dupont in their patent EP 0253310, dated 20 Jan 1988 published a simple route to prepare Losartan but it involves column chromatography for the purification of Cyano alcohol of the formula *(6*), from its regioisomer impurity of the formula (12)

The tetrazole formation from cyano alcohol of the formula (6) takes 13 days for completion. This reaction of the process is shown in the scheme 7.



Scheme 7

Even though Merck-Dupont had number of patents and publications being innovator of the drug, their processes to reach the final drug molecule is lengthy and yields are moderate at some stages. For example in patent US 4820843 dated April 11, 1989, in Example 7, they prepared trityl Losartan of the formula (7) in 21% yield

All the processes described above uses metal azides for the preparation of Tetrazole derivative. Metals such as aluminium (in diethyl aluminium azide) and tin compounds like tri-n-octyl tin azide and trialkyl tin azides are environmentally hazardous chemicals and their disposals are not only cause always problems but also need special methods such as totally recovering the metal from the effluents, which needs ion-exchage chromatography (an additional investment) or complexation techniques.

Hence there is a continuous urge to develop environment friendly and an economical process for the drug Losartan of the formula 1.

Objectives of the invention

Accordingly, the main objective of the present invention is to provide an improved process for the preparation of Losartan of the formula I overcoming the drawbacks of the hitherto known processes.

Another objective of the present invention is to provide an improved process for the preparation of Losartan of the formula I which is simple and environmentally friendly

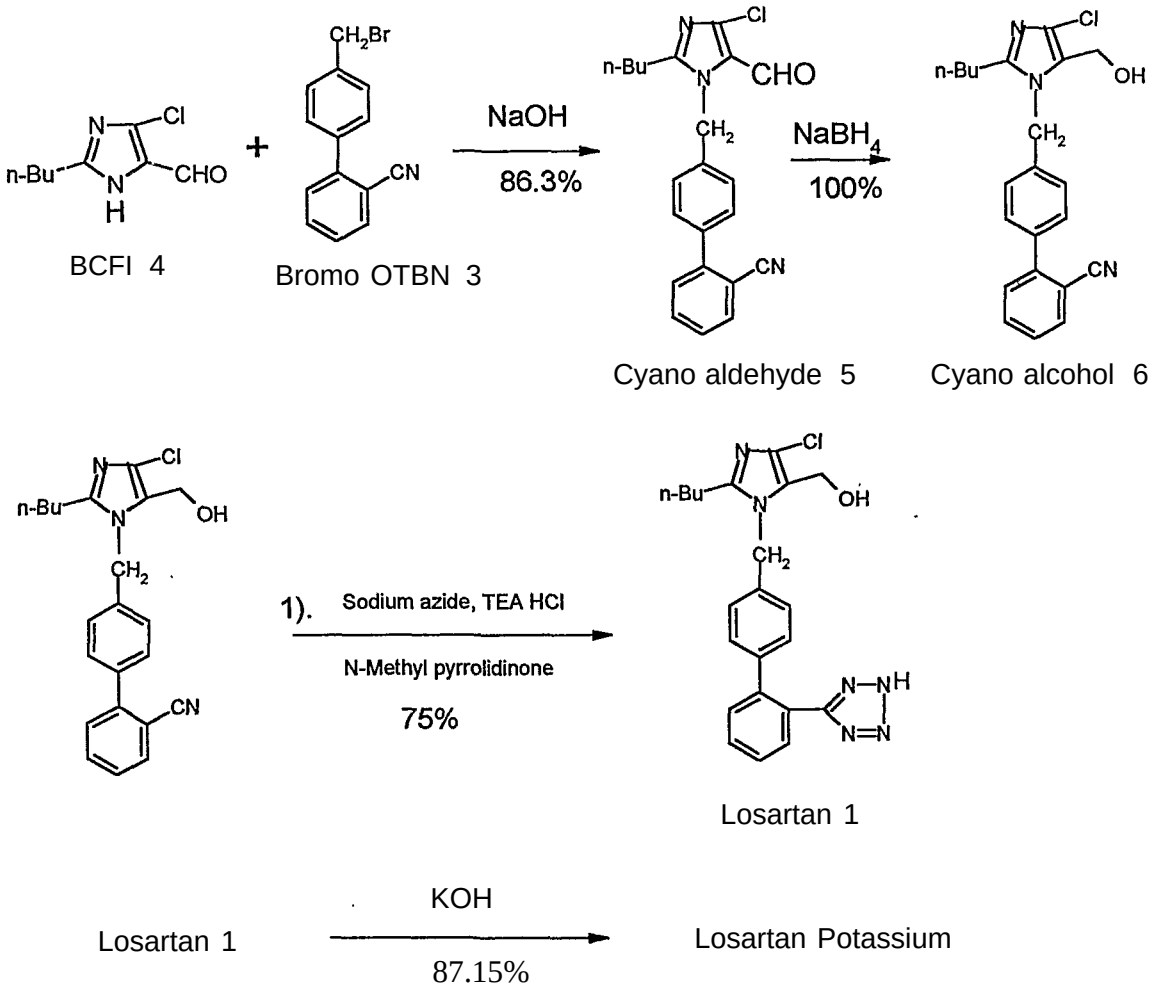
Still another objective of the present invention is to provide an improved process for the preparation of Losartan of the formula I in short reaction times and without employing metal azides and the like.

Yet another objective of the present invention is to provide an improved process for the preparation of Losartan of the formula I in short number of steps to make it economical and with good yields.(> 75%)

The above objectives of present invention have been achieved by avoiding metal azide usage in the preparation of tetrazole derivatives such as Losartan of the formula 1
Such a process is not reported in the literature and makes the process novel

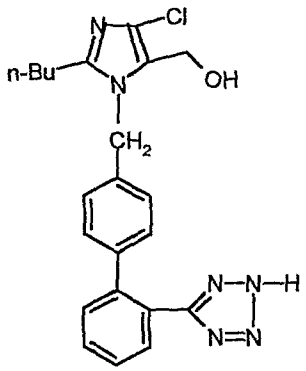
Summary **of the invention**

The reaction scheme of the process of preparing Losartan of the formula I according to he present invention is shown in **Scheme** 8.



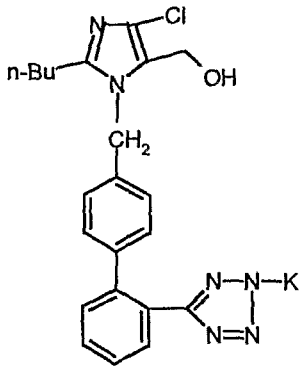
Scheme 8

Accordingly, the present invention provides an improved process for the preparation of Losartan of the formula 1 or its potassium salt of the formula 2 .



LOSARTAN

1



LOSARTAN POTASSIUM

2

Which comprises

(i) Reacting 2-n-butyl-4-chloro-5-formyl imidazole (BCFI)of the fbrmula(4) with 4'-(Bromomethyl)-2-cyanobiphenyl (Bromo OTBN) of the formula (3) in the presence of Phase transfer catalyst to give cyano aldehyde of the formula (5),

(ii) Reducing the cyano aldehyde of the formula (5) so formed with reducing agents to give Cyano alcohol of the formula (6).

(iii) treating the Cyano alcohol of the formula (6) so formed with sodium azide and triethyl amine hydrochloride in a polar aprotic solvents to form Losartan of the formula 1 and if desired

(iv) Converting the formed Losartan of the formula 1 to its potassium salt of the formula 2 by treating it with potassium hydroxide.

The step (i) of the formation of cyano aldehyde may be carried out in the presence of phase transfer catalysts such as Tetrabutyl ammonium bromide (TBAB), or Benzyl triethyl ammonium chloride (TEBAC), Polyethylene Glycol (PEG - 200, 400, 600, 800, 1000 etc.,), preferably Tetrabutyl ammonium bromide (TBAB), or Benzyl triethyl ammonium chloride (TEBAC), and most preferably in Tetrabutyl ammonium bromide (TBAB) to give cyano aldehyde of the formula (5).

In step (ii) the reducing agents may be effected using such as Lithium Aluminium hydride, sodium borohydride , Potassium borohydride preferably low cost Sodium borohydride .

The step (iii) of the formation of tetrazole formation may be carried out in polar aprotic solvents such as DMF_3 DMSO, NMP (N-methyl pyrrolidinone), DMI (dimethyl imidazolidinone) and Dimethyl acetamide, preferably N - methyl pyrrolidinone and DMF and most preferably in N - methyl pyrrolidinone. This step may also carried out in the presence of salts such as pyridine hydrochloride, Triethyl amine hydrochloride, Piperidine acetate, dialkyl amine hydrochloride, preferably in the presence of pyridine hydrochloride or Triethyl amine hydrochloride and most preferably in the presence of Triethyl amine hydrochloride.

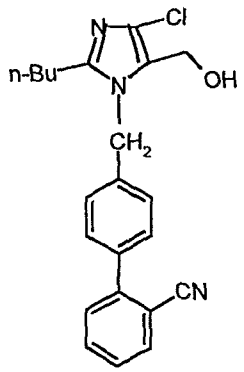
The reaction temperature of step (iii) may be between 90 - 130°C and preferably between 100-120^{0}C and most preferably between 100-110^{0}C. and the reaction period may range between 20-40 hours, preferably 25-30 hours and most preferably between 28-30 hours.

The details of the invention are given in Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of invention.

EXAMPLE- I:

Preparation of Losartan Potassium:

Step (I): Preparation of 2-n-butyl-4-chloro-l-[2'-(cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole of the formula (6) .



6

To a stirred solution of DM Water (360 ml), sodium hydroxide flakes (14.4 gm, 0.36 M) was added toluene (900 ML), Tetrabutyl ammonium bromide (TBAB) (7.2 gm), 4'-(Bromomethyl)-2-cyanobiphenyl (90 gm, 0.33 M) and 2-butyl-4-chloro-5-formyl imidazole (65 gm, 0.34 M) at room temperature (25 - 30°C). The solution was stirred at room temperature for 28-30 hours. After TLC completed the reaction, the organic layer was separated and the aqueous layer was extracted with 200 ml of toluene. The combined organic layers were washed with 150 ml of 7% sodium hydroxide solution and then finally washed with 200 ml of water. Toluene layer was preceded further without isolation of cyano aldehyde of the formula 5 .

To the stirred solution of toluene with compound of the formula 5 (approximately 1200 ml) was added sodium borohydride (12.6 gm, 0.33 M) at room temperature (25 - 30^{0}C). The reaction temperature was raised to 40 - 45°C and methanol was added at 40 - 45°C over a period of 1 hour. After the methanol addition, maintained for 3 hours at 40 - 45°C. After TLC showed the conversion > 99%, it was cooled to 25 - 30^{0}C and 1100 ml of water was added. Further cooled to 10 - 15°C. The cooled solution was filtered and washed with water to get 2-n-butyl-4-chloro-l-[2'-(cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl)-imidazole of the formula of the formula **6** (Yield 86%)

Melting point: 154 - 156°C.

HPLC Purity. > 98%

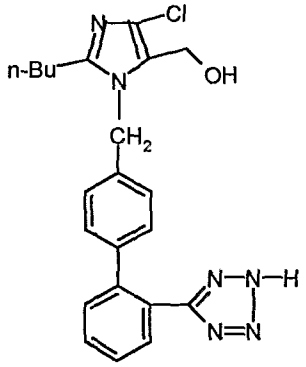
IR. v max (KBR): 3275.27 (- CH_2OH), 2221 (- CN),

^{1}H **NMR** (CDC13) δ , 0.88 (t, 3H), 1.35 (sext, 2H), 1.69 (quint, 2H), 2.6 (t, 2H), 4.51 (s, 2H), 5.30 (s, 2H), 7.1 1 - 7.77 (m, 8H).

^{13}C **NMR** (CDC13) δ , 13.64, 22.30, 26.63, 29.60, 47.11, 52.85, 111.05, 118.47, 124.99, 126.2, 127.0, 127.7, 129.29, 129.9, 132.8, 133.7, 136.72, 137.65, 144.52, 148.5

MS (m/z) = 380.2 (M+l).

Step—II: Preparation of 2-n-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl] imidazole [Losartan] of the formula (1)



1

To a stirred solution of 2-n-butyl-4-chloro-l-[2'-cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl) imidazole (105 gm, 0.276 M) prepared by the process described in step I in 210 ml of N-methyl pyrrolidinone at room temperature was added Triethyl amine hydrochloride (75 gm, 0.545 M) and sodium azide (35 gm, 0.54 M) at room temperature (25 — 30°C). The reaction temperature was raised to 103-105 ^{0}C and maintained for 28-30 hours. TLC showed the absence of starting material.

The reaction mixture was cooled to 45 - 50°C and charged 300 ml of toluene, 800 ml of water with stirring. The organic layer was separated and 'aqueous layer was washed with 250 ml of toluene. The aqueous layer was treated with 10 grams of activated carbon and filter through celite. Aqueous layer PH was adjusted to 4.3-4.5 with acetic acid (70 - 75 ml) and was stirred for 8 hours at 25 - 30^{0}C. The aqueous solution was filtered and washed with water to get the Losartan of the formula **(1).** (Yield: > 75%).

Melting point: 180.5 - 181.2

HPLC Purity: > 98%

IR v max (KBR): 3376.27 , 1579.77, 1468.86, 762.88, 556.4

^{1}H **NMR** (CDC13) δ , 0.87 (t, 3H), 1.31 (sext, 2H), 1.54 (quint, 2H), 2.57 (t,2H), 4.45 (s,2H), 5.30 (s,2H), 7.01 - 7.68 (m, 8H).

^{13}C **NMR** (CDC13) δ , 14.07, 23.24, 27.40, 30.92, 126.71, 126.86, 127.35, 128.21, 130, 130.8, 131, 131.19, 131.81, 136.09, 142.21, 149.97, 162.72

M S (m/z) = 423.5 (M+l).

Step-Ill: Preparation of 2-n-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yI)methyl] imidazole: Potassium salt of Losartan of the formula (2).

To a stirred solution of 2-n~buryl-4-cl ℑoro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl] imidazole (Losartan of the formula (I)) obtained in step II (50 gm, 0.118 M) in 250 ml of methanol was added potassium hydroxide powder [7.6 gm (86%), 0.1 18 3VTj at room temperature (25 - 30°C). The reaction temperature was raised to reflux (60 - 63°C) and maintained for 4-5 hours at 60 - 63°C. The reaction mixture was cooled to 35 - 40°C. This was filtered through celite and the clarified solution was concentrated to remove most of methanol at 45 - 5O^{0}C under reduced pressure. 100 ml of Methyl ethyl ketone was added and distillation continued to distill most of the methanol/methyl ethyl ketone mixture. Residue was diluted with 200 ml of Acetone and contents cooled to 5 - 10°C for 30 minutes and product filtered and washed with 50 ml of acetone. Product was dried under reduced pressure to yield 47.5 grams. (87.15% of theory) of Losartan Potassium of the formula **(2).**

HPLC Purity. 99.81%.

IR. v max (KBR): 3201.01 , 1580.73, 1460.18, 764.81, 540.09

'H **NMR** (MeOD) δ, 0.87 (t, 3H), 1.33 (sext, 2H), 1.53 (quint, 2H), 2.56 (t,2H), 4.43 (s,2H), 5.24 (s,2H), 6.89 - 7.53 (m, 8H).

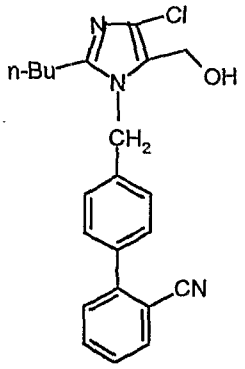
^{13}C **NMR** (MeOD) δ, 14.07, 23.24, 27.40, 30.92, 126.71, 126.86, 127.35, 128.21, 130, 130.8, 131, 131.19, 131.81, 136.09, 142.21, 149.97, 162.72

M S (m/z) = 423.3 (M+l).

EXAMPLE - 2:

Preparation of Losartan Potassium:

Step (I): Preparation of 2-n-butyI-4-chloro-l-[2'-(cyanobiphenyl-4-yl)methyI]-5-(hydroxymethyl)-imidazole of the formula 6 .



6

To a stirred solution of DM Water (360 ml), sodium hydroxide flakes (14.4 gm, 0.36 M) was added toluene (900 ML), Benzyl triethyl ammonium chloride (TEBAC) (7.2 gm), 4'-(Bromomethyl)-2-cyanobiphenyl (90 gm, 0.33 M) and 2-butyl-4-chloro-5-formyl imidazole (65 gm, 0.34 M) at room temperature (25 - 30^0C). The solution was stirred at room temperature for 28-30 hours. After TLC completes the reaction, the organic layer is separated and the aqueous layer is extracted with 200 ml of toluene. The combined organic layers were washed with 150 ml of 7% sodium hydroxide solution and then finally washed with 200 ml of water. Toluene layer is proceed further without isolation of cyano aldehyde of the formula 5 .

To the stirred solution of toluene with compound of the formula 5 (approximately 1200 ml) was added sodium borohydride (12.6 gm, 0.33 M) at room temperature (25 - 30^0C). The reaction temperature was raised to *40* —45°C and methanol was added at 40 - 45°C over a period of 1 hour. After the methanol addition, maintained for 3 hours at 40 - 45°C. After TLC showed the conversion > 99%, it was cooled to 25 – 30^0C and 1100 ml of water was added. Further cooled to 10 - 15°C. The cooled solution was filtered and washed with water to get the cyano alcohol of the formula **(6).** (Yield 86%)

Melting point: 154 - 156°C.

HPLC Purity: > 98%

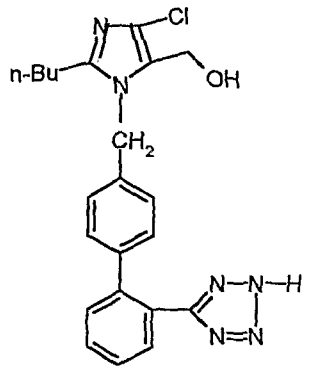
IK. v max (KBR): 3275.27 (- CH_2OH), 2221 (- CN),

^{1}H NMR (CDC13) δ , 0.88 (t, 3H), 1.35 (sext, 2H), 1.69 (quint, 2H), 2.6 (t, 2H), 4.51 (s, 2H), 5.30 (S. 2H), 7.1 1 - 7.77 (m, 8H).

^{13}C **NMR** (CDC13) δ , 13.64, 22.30, 26.63, 29.60, 47.11, 52.85, 111.05, 118.47, 124.99, 126.2, 127.0, 127.7, 129.29, 129.9, 132.8, 133.7, 136.72, 137.65, 144.52, 148.5

MS (m/z) = 380.2 (M+l).

Step-π: Preparation of 2-n-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl] imidazole [Losartan] of the formula I :



1

)

To a stirred solution of 2-n-butyl-4-cMoro-l-[2'-cyanobiphenyl-4-yl)methyl]-5-(hydroxymethyl) imidazole (105 gm, 0.276 M) prepared by the process described in step I in 210 mi of N-methyl pyrrolidinone at room temperature was added TEA HCl (75 gm, 0.545 M) and sodium azide (35 gm, 0.54 M) at room temperature (25 - 30^0C). The reaction temperature was raised to 103-105°C and maintained for 28-30 hours. TLC showed the absence of starting material.

The reaction mixture was cooled *to* 45 - 50°C and charge 300 ml of toluene, 800 ml of water with stirring. The organic layer was separated and aqueous layer was washed with 250 ml of toluene. The aqueous layer is treated with 10 grams of activated carbon and filter through celite. Aqueous layer PH was adjusted to 4.3-4.5 with acetic acid (70 - 75 ml) and was stirred for 8 hours at 25 - 30°C. The aqueous solution was filtered and washed with water to get Losartan of the formula 1. (Yield: > 75%).

Melting point: 180.5 - 181.2

HPLC Purity: > 98%

IR. v max (KBR): 3376.27 , 1579.77, 1468.86, 762.88, 556.4

^1H **NMR** (CDC13) δ , 0.87 (t, 3H), 1.31 (sext, 2H), 1.54 (quint, 2H), 2.57 (t,2H), 4.45 (s,2H), 5.30 (s,2H), 7.01 - 7.68 (m, 8H).

^{13}C **NMR** (CDC13) δ , 14.07, 23.24, 27.40, 30.92, 126.71, 126.86, 127.35, 128.21, 130, 130.8, 131, 131.19, 131.81, 136.09, 142.21, 149.97, 162.72

M S (m/z) = 423.5 (MH-I).

Step-Ill: Preparation of 2-n-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl] imidazole: Potassium salt of Losartan formula (2).

To a stirred solution of 2-n-butyl-4-chloro-5-hydroxymethyl-l-[(2'-(lH-tetrazole-5-yl)biphenyl-4-yl)methyl] imidazole (Losartan *T)* obtained by the process described in step π (50 gm, 0.118 M) in 250 ml of methanol was added potassium hydroxide powder [7.6 gm (86%), 0.118 M] at room temperature (25 - 30°C). The reaction temperature is raised to reflux (60 - 63°C) and maintained for 4-5 hours at 60 - 63°C. The reaction mixture was cooled to 35 - 40^{0}C. This was filtered through celite and the clarified solution was concentrated to remove most of methanol at 45 - 50^{0}C under reduced pressure. 100 ml of Methyl ethyl ketone was added and distillation continued to distill most of the methanol/methyl ethyl ketone mixture. Residue was diluted with 200 ml of Acetone and contents cooled to 5 - 10^{0}C for 30 minutes and product filtered and washed with 50 ml of acetone. Product was dried under reduced pressure to yield 47.5 grams. (87.15% of theory) Losartan Potassium of he formula **(2).**

HPLC Purity: **99.82%.**

IR v max (KBR): 3201.01 , 1580.73, 1460.18, 764.81, 540.09

^{1}H **NMR** (MeOD) δ , 0.87 (t, 3H), 1.33 (sect, 2H), 1.53 (quint, 2H)$_5$ 2.56 (t,2H), 4.43 (s,2H), 5.24 (s,2H), 6.89 - 7.53 (m, 8H).

^{13}C **NMR** (MeOD) δ , 14.07, 23.24, 27.40, 30.92, 126.71, 126.86, 127.35, 128.21, 130, 130.8, 131, 131.19, 131.81, 136.09, 142.21, 149.97, 162.72

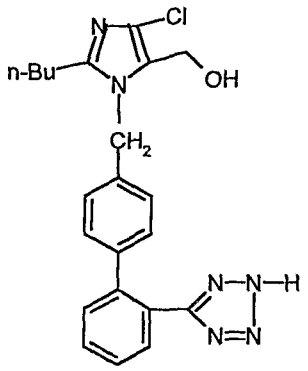
M S (m/z) = 423.3 (M+l).

Advantages of the invention

1. The process does not use reagents such as heavy metal azides, tri-n-butyl tin azide, and tri-n-Octyl tin azide, therefore environmentally safe.
2. Consequently there is no disposal problems
3. The process is easy to perform and in less number of steps and hence economical.
4. The yield of Losartan produced is enhanced (>75%) and the purity of (*>99 %*)
5. The process is commercially applicable.

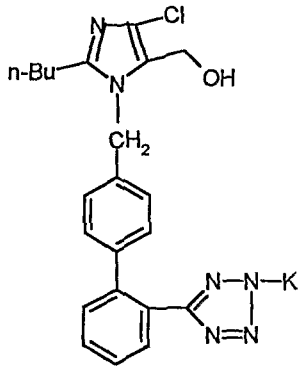
WE CLAIM

1. An improved process for the preparation of Losartan of the formula 1 or its potassium salt of the formula 2



LOSARTAN

1



LOSARTAK POTASSIUM

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Which comprises

(i) reacting 2-n-butyl-4-chloro-5-formyl imidazole (BCFI) of the formula (4) with 4'-(Bromomethyl)-2-cyanobiphenyl (Bromo OTBN) of the formula (3) in the presence of phase transfer catalyst to give cyano aldehyde of the formula (5),

(ii) reducing the cyano aldehyde of the formula (5) so formed with reducing agents to give Cyano alcohol of the formula (6).

(iii) treating the Cyano alcohol of the formula (6) so formed with sodium azide and triethyl amine hydrochloride in a polar aprotic solvents to form Losartan of the formula 1 and if desired

(iv) Converting the formed Losartan of the formula 1 to its potassium salt of the formula 2 by treating it with potassium hydroxide.

2. An improved process as claimed in claim1 wherein the step (i) of the formation of cyano aldehyde is carried out in the presence of phase transfer catalysts such as Tetrabutyl ammonium bromide (TBAB), or Benzyl triethyl ammonium chloride (TEBAC), Polyethylene Glycol (PEG - 200, 400, 600, 800, 1000 etc.,), preferably Tetrabutyl ammonium bromide (TBAB), or Benzyl triethyl ammonium chloride (TEBAC), and most preferably in Tetrabutyl ammonium bromide (TBAB) to give cyano aldehyde of the formula (5).

3. An improved process as claimed in claims 1 & 2 wherein in step (ii) the reducing agents such as Lithium Aluminium hydride, sodium borohydride , Potassium borohydride preferably low cost Sodium borohydride is used

4. An improved process as claimed in claims 1-to 3 wherein in the step (iii) the polar aprotic solvents such as DMF, DMSO, NMP (N-methyl pyrrolidinone), DMI (dimethyl imidazolidinone) and Dimethyl acetanüde, preferably N - methyl pyrrolidinone and DMF and most preferably in N - methyl pyrrolidinone is used

5. An improved process as claimed in claims 1 to 4 wherein in the step (iii) is carried out in the presence of salts such as pyridine hydrochloride, Triethyl amine hydrochloride, Piperidine acetate, dialkyl amine hydrochloride, preferably in the presence of pyridine hydrochloride or Triethyl amine hydrochloride and most fSreiefably in the presence of Triethyl amine hydrochloride.

6. An improved process as claimed in claims 1 to 3 wherein in the step (iii) is effected at a temperature between 90 - 130°C, preferably between 100-120°C and most preferably between 100-1 10°C

7. An improved process as claimed in claims 1 to 5 wherein in the step (iii) is effected for a period in the range between 20-40 hours, preferably 25-30 hours and most preferably between 28-30 hours.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2005/000426

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/10

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)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to claim No
A	WO 2005/014602 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; SEDELMEIER, GOTTFRIED) 17 February 2005 (2005-02-17) cited in the application page 51above, cf. schemed aims	1-7
A	EP 0 578 125 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 12 January 1994 (1994-01-12) cited in the application claims 6-17; example 8	1-7

D Further documents are listed In the continuation of Box C

[X] See patent family annex

* Special categories of cited documents

"A[1] document defining the general state of the art which is not considered to be of particular relevance

[1]E[1] earlier document but published on or after the intθrnatlonal filing date

[1]L" document which may throw doubts on prionty claiφ) 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

[1]P[1] document published prior to the international filing date but later than the priority date claimed

[1]T[1] later document published after the international filing date or pnority 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 alons

"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 docu¬ments, such combination being obvious to a person stalled 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
8 May 2006	17/05/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016	Schmid, A

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INTERNATIONAL SEARCH REPORT

Information on patent family memberβ

International application No
PCT/IN2005/000426

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