An improved novel process for the synthesis of antihypertensive drug, Irbesartan

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Un nuevo procedimiento mejorado para la síntesis del fármaco antihipertensivo irbesartán

Nou procediment millorat per a la síntesi del fàrmac antihipertensiu Irbesartán

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RESUMEN

En general tetrazoles 5-sustituidos se prepararon a través de reacciones de azida de sodio con nitrilos en un disolvente aromático en presencia de una sal de amina. El presente trabajo describe el proceso para la preparación de la 2-butil-3-[[2'-(1H-tetrazol-5-il) [1,1'-bifenil]-4-il] metil]-1,3-diazaespiro [4.4] non-1-en-4-ona [Irbesartán] por reacción de la correspondiente 2-butil-3-[(2'-cianobifenil)-4-il] metil-1,3-diazaespiro [4.4] non -1-eno con una azida de sodio y clorhidrato de dimetilamina.

Palabras clave: Tetrazole; azida de sodio, sales de dimetilamina; bifenilo ciano; irbesartán.

SUMMARY

In general 5-substituted tetrazoles were prepared through the reactions of sodium azide with nitriles in an aromatic solvent in the presence of an amine salt. The present work describes process for the preparation of the 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one [Irbesartan] by reaction of the corresponding 2-butyl-3-[(2'-cyanobiphenyl)-4-yl] methyl-1,3-diazaspiro[4.4]non-1-ene with an sodium azide and dimethylamine hydrochloride.

Key words: Tetrazole; sodium azide; dimethylamine salts; cyano biphenyl; Irbesartan.

RESUM

En general tetrazols 5-substituïts es van preparar mitjançant reaccions d'azida de sodi amb nitrils en un dissolvent aromàtic en presència d'una sal d'amina. Aquest treball descriu el procés per a la preparació de la 2-butil-3-[[2'-(1H-tetrazol-5-il) [1,1'-bifenil]-4-il] metil]-1,3-diazaespiro [4.4] non-1-en-4-ona [irbesartán] per reacció de la corresponent 2-butil-3-[(2'-cianobifenil)-4-il] metil-1,3-diazaespiro [4.4] non-1-è-4-ona amb una azida de sodi i clorhidrat de dimetilamina.

Mots clau: Tetrazol; azida de sodi, sals de dimetilamina, cianobifenil, irbesartan.

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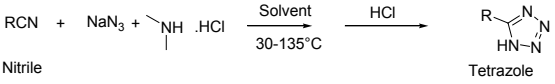
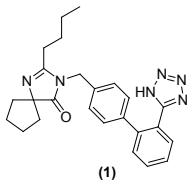
INTRODUCTION

Tetrazole derivatives have attracted much attention as raw materials for medicine, agricultural chemicals, foaming agents, and in the automobile inflator industry.[1-4] Several methods for the synthesis of tetrazoles have been reported, but these conventional methods for the synthesis of tetrazoles have several disadvantages. e.g. the synthetic method that uses amine salts in dimethylformamide (DMF)[5–7] is laborious and due to the formation of byproducts; this method is applicable only to the synthesis of tetrazoles starting from simple nitriles. The synthetic method using NH_4Cl in DMF[8, 9] also has disadvantages, as the reaction is accompanied by the sublimation of highly dangerous explosive NH_4N_3. Method that uses acid for the synthesis of tetrazole,[10] the reaction proceeds relatively slow at room temperature and is also dangerous due to the production of poisonous and explosive HN_3. Aromatic solvents and organostannane catalysts are often used for the preparation of tetrazole compounds having polyfunctional groups from the respective nitriles.[11–12] Stannane compounds used in these reactions are generally highly toxic and it is often difficult to completely separate the desired tetrazole from the stannane compounds.

A versatile method for synthesizing many kinds of tetrazoles through safe and simple manipulation is shown below

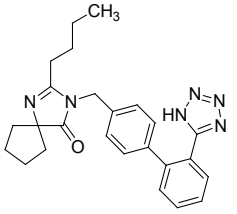


Irbesartan[13] belongs to the class of drug called angiotensin II receptor antagonist antihypertensives. It is used to treat high blood pressure (hypertension), and it is also used to treat kidney problems caused by type 2 (non insulin-dependent) diabetes. The current pharmaceutical product containing this drug is being sold by Sanofi Synthelabo using the trade name AVAPRO, in the form of tablets. Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[[2'-(1*H*-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]-1,3-diazaspiro[4.4]non-1-en-4-one. Its empirical formula is $C_{25}H_{28}N_6O$ and the structural formula:



(1)

Various processes for preparation of N-substituted heterocyclic derivatives and their salts was disclosed in U.S. Patent No. 5,270,317.[14] These compounds are angiotensin II antagonist that is especially useful in the treatment of cardiovascular ailments such as hypertension and heart failure, as well as in preventing disorders of central nervous system, glaucoma, diabetic retinopathy, and diabetic nephropathy. As per the process described in the U.S. patent 5,270,317 Irbesartan is prepared by reaction of 2-n-butyl-1, 3-diazaspiro[4,4]non-1-en-4-one hydrochloride **(3)** with 4-bromomethyl-2'-cyanobiphenyl **(2)** in the presence of sodium hydroxide, followed by a column chromatography separation to produce 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo- lin-5-one **(4)**, which upon reaction with tributyltin azide and trityl chloride followed by deprotection with HCl produce Irbesartan **(1).**



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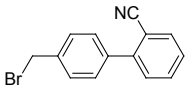

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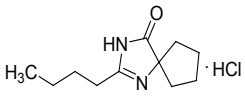

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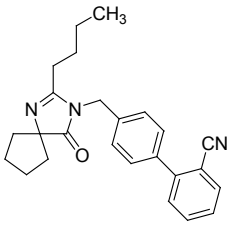


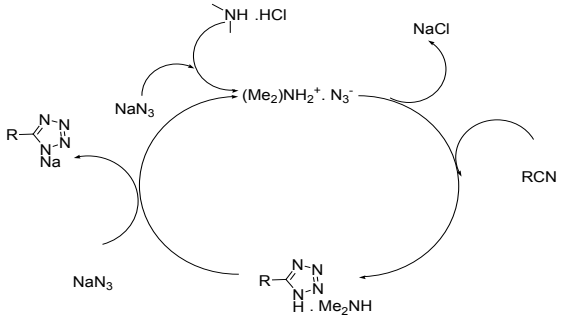
(4)

Irbesartan obtained by the process described in the 5,270,317 patent may not have satisfactory purity. Unacceptable amounts of impurities may be formed along with Irbesartan. The yield of Irbesartan obtained is very poor and the process involves column chromatographic purifications; which are generally undesirable for large-scale operations, thereby making the process commercially unfeasible.

A process for the preparation of Irbesartan is reported wherein 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one is treated with sodium azide in the presence of triethylamine hydrochloride in an inert polar aprotic solvent such as 1-methylpyrrolidin-2-one at a temperature of 121-123°C.[14] The solvent used is costly and not easily recovered thereby making the process unsuitable for commercial scale production. Isolation of Irbesartan from the reaction mixture is tedious and requires several critical layer separations and layer filtrations. Moreover, unacceptable amounts of impurities are formed along with Irbesartan, thus resulting in a poor product yield. Deshpande et.al.[15] describes a process for the preparation of Irbesartan wherein 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one is treated with sodium azide in the presence of triethylamine and acetic acid. In literature [16] also disclosed the process for the preparation of tetrazole protected Irbesartan from aromatic nitrile derivative in the presence of a protecting group, trialkyltin azide and o-xylene. In all these processes Irbesartan synthesized using an organotin compound, which is difficult to remove and remains in the product as an impurity which is undesirable for Irbesartan. Several other synthetic routes have been described in the literature for the preparation of Irbesartan. Most of the routes comprise the reaction of a 4-bromomethyl-2'-cyanobiphenyl compound with 2-n-butyl-1,3-diazaspiro[4,4] non-1-en-4-one hydrochloride.[17-20] The last step in most of the processes corresponds to the formation of the tetrazole ring from a cyano group employing an azide derivative. An improved method for synthesis of Irbesartan has been described by K.V.V. Prasad Rao.[21] Koguro et.al.[22] prepared variety of 5-substituted tetrazoles by reaction of nitriles

with sodium azide in an aromatic solvent in the presence of amine salt.

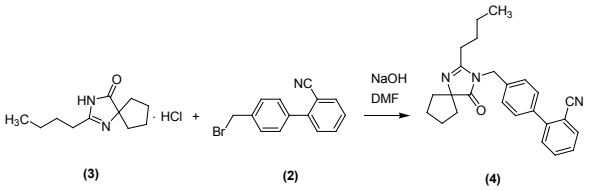
To resolve the problems associated with the processes described in the prior art, there remains need for an improved and commercially viable process of preparing a substantially pure Irbesartan, which will be suitable for large-scale preparation. For this reason processes which can afford Irbesartan, which must be free from any amount of tin content and its analogues which can be an environmental hazard when employed as a medicament, are highly desirable. Processes should include non-hazardous and environmental friendly reagents, reduces cost of manufacturing, greater simplicity, increase purity, and increases yield of the product.



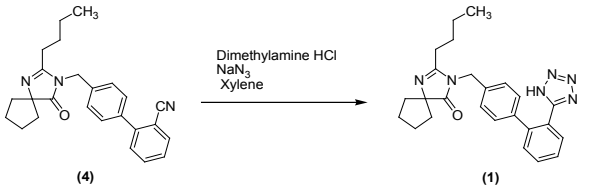
RESULTS AND DISCUSSION

The present invention describes the process for preparation of the Irbesartan **(1)** from its penultimate intermediate **(4)** using dimethylamine hydrochloride and sodium azide. Said intermediate **(4)** is formed by the reaction between 4-bromomethyl-2'-cyanobiphenyl **(2)** and 2-n-butyl-1,3-diazaspiro[4,4]non-1-en-4-one hydrochloride **(3)**.

Stage 1: Preparation of Intermediate for Irbesartan



Stage 2: Preparation of Irbesartan



The above mentioned reaction is carried out in presence of suitable solvents and chemical reagents. The final product is substantially pure Irbesartan.

Various process parameters were optimized and the optimum parameters for synthesis of **stage-1 (4)** and **stage-2 (1)** are as:

For Stage-1: 4-bromomethyl-2'-cyanobipheny (2) – 1.05 Mole; 2-n-butyl-1,3-diazaspiro[4,4]non-1-en-4-one hydrochloride (3) – 1.0 Mole; DMF – 4.5 Volume; NaOH – 2.3 Mole; Temperature – 30-35°C

For Stage-2: 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one (4) – 1 Mole; Xylene / n-Butanol - 3 Volume; NaN_3 – 2.5 Mole; Dimethylamine HCl – 3.5 Mole; Temperature - 115-120°C

The tentative mechanism for this reaction is shown below, in analogy with mechanism reported for tetrazole formation using triethyl amine[22]

EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and used without purification. Melting points were determined on a Veggo VMP-2 melting point apparatus. All the melting points were taken in an open capillary and uncorrected. The IR spectra were recorded in solid state as KBr dispersion using a Perkin-Elmer FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300-MHz spectrometer. The chemical shifts are reported in δ parts per million (ppm) relative to TMS. The mass spectra were recorded on an API 2000 Perkin-Elmer PE-SCIEX mass spectrometer.

Preparation of 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one (4)

In a 3 L 3-necked flask, equipped with stirrer, thermometer and reflux condenser, 2-n-butyl-1,3-diazaspiro[4,4] non-1-en-4-one hydrochloride (3) (100 g) was mixed with Dimethylformamide (500 mL) at temperature 30°C – 35°C. 40 g of NaOH is charged in single lot. Reaction mixture is stirred for 30 min. 4-bromomethyl-2'-cyanobiphenyl (2) (112 g) was added in to the reaction mixture and stirred for 12 h at the same temperature. To the mixture was added water (1120 mL) and toluene (560 mL) and stirred for 30 min. Layers were separated and toluene layer after water wash subject to distillation. After complete removal of solvent petroleum ether (50 mL) is added to residue and again distilled completely. Petroleum ether (342 mL) is added to residue and stirred for 1 h. Reaction mass was chilled at 0°C - 5°C and maintained for 2 h, filtered and washed. Wet-cake was dried at 50°C – 55°C for 10 – 12 h.

Dry weight of product: 150 g

Purification of Irbesartan intermediate (4) [23]

In a 3 L 3-necked flask, equipped with stirrer, thermometer and reflux condenser, -[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one (4) (100 g) was charged with Isopropyl alcohol (150 mL) and DM water (225 mL) at 30°-32°C. Resultant mixture was stirred for 90 minutes. Cool to 0-5°C and stir for 30-45 minutes. Filter the solid and was wash it with chilled isopropyl alcohol (38 mL) and DM water (56 mL). Suck dry for 15 minutes and dry the product under vacuum (about 10 mmHg) at 45-50°C.

Dry weight of product: 90 g

IR (KBr, cm^{-1}): 2220.72 (CN stretching), 1720.08 (C=O amide stretching), 1628.73 (C=N stretching); **Mass:** MS(EI)

calculated for $C_{25}H_{28}N_3O$ ($M^+ + 1$) : 386.22, observed value : 386.22 ; **^{1}H-NMR** ($CDCl_3$) δ 7.77 (d, J=7.6 Hz, 1H), 7.65 (td, J=1.1, J=7.7 Hz,1H), 7.54 (J=4.1 Hz, 2H), 7.49 (d, J=7.6Hz, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.28 (d, J=8.10Hz,2H), 4.75 (s, 2H), 2.35 (t, J=7.8 Hz, 2H), 2.06-1.93 (m, 6H), 1.88-1.84 (m, 2H), 1.60 (quintet, J=7.4 Hz,2H), 1.34 (sextet, J=7.4 Hz, 2H), 0.88 (t, J=7.3 Hz, 3H); **^{13}C-NMR** ($CDCl_3$) 186.8, 161.5, 144.7, 137.7, 137.2, 133.8, 132.9, 132.0, 129.4, 127.7, 127.1, 118.6, 111.2, 76.6, 43.3, 37.5, 28.8, 27.8, 26.1, 22.3, 13.7.

Preparation of Irbesartan (1)
In a 3 L 3-necked flask, equipped with stirrer, thermometer and reflux condenser, charged n-Butanol (300 mL) and 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one (4) (100 g). To the reaction mixture is added Dimethyl amine hydrochloride (74 g) and Sodium azide (42.5 g). Mixture was stirred for 30 minutes at a temperature of 30°C. Slowly temperature was raised to 115-120°C and maintained for 24 h. The reactant mass was cooled to 30-32°C and water (250 mL), 30% Sodium hydroxide and Sodium nitrite were added and stirred for 30 minutes. Aqueous layer was separated and washed with n-Butanol (50 ml). 25 mL Ethyl Acetate added to aqueous layer and adjusted pH 3.0 – 4.0 using 6N hydrochloric acid. Reaction mass filtered and wet-cake washed with water (300 mL). To wet cake was added 1500 mL Isopropyl alcohol and refluxed till clear reaction mass. After charcoalization filtrate was distilled to half volume under reduced pressure. Resultant mass was chilled at 0 - 5°C, Maintain for 2 h at same temperature and Filtered. Wet cake dried under vacuum of about 10 mmHg.
HPLC purity – 99.0%; Dry weight of product: 70 g

Preparation of Irbesartan (1)
In a 3 L 3-necked flask, equipped with stirrer, thermometer and reflux condenser, charged Xylene (300 mL) and 1-[(2'-cyanobiphenyl-4-yl) methyl]-2-n-butyl-4-spirocyclopentane-2-imidazo-lin-5-one (4) (100 g). To the reaction mixture is added Dimethyl amine hydrochloride (74 g) and Sodium azide (42.5 g). Mixture was stirred for 30 minutes at a temperature of 30°C. Slowly temperature was raised to 115-120°C and maintained for 24 h. The reactant mass was cooled to 30-32°C and water (250 mL), 30% Sodium hydroxide (60 mL) and 30 % aqueous Sodium nitrite (60 mL) were added and stirred for 30 minutes. Aqueous layer was separated and washed with Xylene (50 mL). 25 mL Ethyl Acetate added to aqueous layer and adjusted pH 3.0 – 4.0 using 6N hydrochloric acid. Reaction mass filtered and wet-cake washed with water (300 mL). To wet cake was added 1500 mL Isopropyl alcohol and refluxed till clear reaction mass. After charcoalization filtrate was distilled to half volume under reduced pressure. Resultant mass was chilled at 0 - 5°C, Maintain for 2 h at same temperature and Filtered. Wet cake dried under vacuum of about 10 mmHg.
HPLC purity – 99.0% ; Dry weight of Product: 70 g

Analysis Data:
Melting Point: 180–182°C;

IR Data: (KBr, cm^{-1}): NH 3447, CO 1733; **NMR Data: ^{1}H NMR :** (DMSO d6): δppm 0.7–0.9 (t, 3H, CH_3), 1.17–1.40 (sextet, 2H, CH_2), 1.40–1.60 (quintet, 2H, CH_2) 1.60–2.00 (m, 8H, cyclopentyl), 2.2–2.4 (t, 2H, CH_2), 4.60–4.80 (s, 2H, Ar-CH_2), 7.32–7.95 (m, 8H, biphenyl); **^{13}C NMR:** 14.5, 22.4, 26.3, 27.4, 28.3, 37.7, 43.1, 76.7, 124.3, 127.1, 128.7, 130.1, 131.4, 131.9, 137.2, 139.2, 141.9, 155.9, 162.0, 186.5; **Mass:** MS(EI) calculated for $C_{25}H_{28}N_6O$ ($M^+ + 1$) :428.53, observed value : 429.53; **CHN** Analysis calculated for $C_{25}H_{28}N_6O$: 70.07, 6.59, 19.61. Found: 70.35, 6.61, 19.61.
Heavy metal: Less than 10 PPM

CONCLUSIONS

The present invention provides an improved process for the preparation of Irbesartan which is succinct, direct and industrially feasible. It also provides a process which eliminates the use of chromatographic purification at intermediate stages, which is not feasible for commercial scale production. Yield and purity of Irbesartan is significantly high. We have successfully avoided use of costly and environmentally hazardous solvent / chemical reagents. Finally Irbesartan produce from this process is free from tin content.

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