SYNTHESIS AND CHARACTERIZATION OF IRBESARTAN IMPURITIES

B. Satyanarayana, Y. Anjaneyulu[1], P. Veerasomaiah[2], P. Pratap Reddy*
Research and Development Centre, Dr Reddy's Laboratories Limited,
Bulk Actives Unit IV, IDA, Jeedimetla, Hyderabad, AP, India-506 055
Ph. No. 91 40 23098610, E-mail: reddvppou@vahoo.co.in
[1]Department of Chemistry, JNTU, Hyderabad
[2]Department of Chemistry, Osmania University, Hyderabad
DRL Pub. No. IPDO-IPM 00020

Abstract : In the course of synthesis of an antihypertensive drug, Irbesartan, five process related potential impurities were detected by using high performance liquid chromatography. They were synthesized and characterized by NMR, Mass, and IR. Synthesis and characterization of these Irbesartan impurities is reported.

Introduction

Antihypertensives are one of the most diverse and commercially successful class of drugs of recent years. Of the various known antihypertensive drugs, sartans gained immense significance. They control blood pressure by blocking the action of angiotensin. Irbesartan (1), one among the class of angiotensin receptor blockers, functions as a specific and competitive angiotensin I receptor antagonist. Recently, we have reported a new and scalable synthetic route for the preparation of Irbesartan (2). For an effective large scale API production and its commercialization in regulated markets, it becomes essential to have knowledge of the impurity profile of the drug substance. In this context, we have identified, synthesized and characterized five potential process related impurities. In this present article, we herewith disclose our work regarding the synthesis and characterization of the impurities of Irbesartan.

Discussion

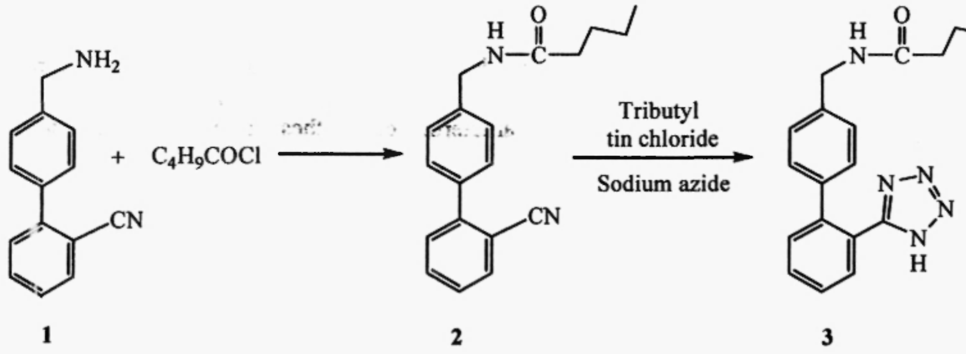
Pentanoic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **2**, pentanoic acid (2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amide **3**, *N*-(2'-cyano-biphenyl-4-yl-methyl)-2, 2, 2-trifluoro-acetamide **4**, 2, 2, 2-trifluoro-*N*-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-acetamide **5** and 3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1, 3-diaza-spiro [4,4] non-1-en-4-one **9** are the different process related impurities encountered during the synthesis of Irbesartan.

Pentanoic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (2)

4'-Aminomethyl-biphenyl-2-carbonitrile (3) **1** was taken as the starting material for the preparation of pentanoic acid (2'-cyano-biphenyl-4-yl-methyl)-amide **2**. Reaction of 4'-aminomethyl-biphenyl-2-carbonitrile **1** with pentanoyl chloride resulted in the formation of pentanoic acid (2'-cyano-biphenyl-4-yl-methyl)-amide **2** (Scheme 1). The EI mass spectrum displayed the molecular ion of **2** at m/z 293. IR spectrum showed the presence of NH, CN, C=O groups at 3300.9, 2224.1, and 1645.6 reapectively.

Pentanoic acid (2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amide (3)

Pentanoic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **2** on reaction with tributyl tin chloride and sodium azide in the presence of xylene as solvent yielded pentanoic acid (2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amide **3** (Scheme-1). The molecular ion of **3** appeared as the base peak at m/z 336 in the EI mass spectrum. IR spectrum showed the presence of two NH and C=O groups at 3280.7, 3101.6 and 1634.1 respectively. The methylene proton attached to the nitrogen appeared as a singlet at 4.5-4.7 δ whereas the aromatic protons gave a multiplet at 7.4-7.9 δ.



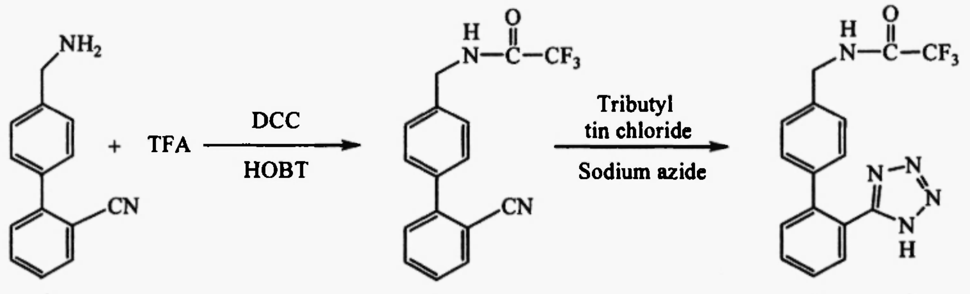
Scheme-1

N-(2'-Cyano-biphenyl-4-yl-methyl)-2, 2, 2-trifluoro acetamide (4)

Reaction of 4'-aminomethyl-biphenyl-2-carbonitrile **1** with trifluoro acetic acid in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxy benzotriazole (HOBT) yielded *N*-(2'-cyano-biphenyl-4-ylmethyl)-2, 2, 2-trifluoro acetamide **4** (Scheme-2). The EI mass spectrum displayed the molecular ion of **4** at m/z 305. The presence of 3294.3 (NH), 2227.0 (CN) and 1701.4 (C=O) was evident in the infra-red spectrum.

2, 2, 2-Trifluoro-N-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-acetamide (5)

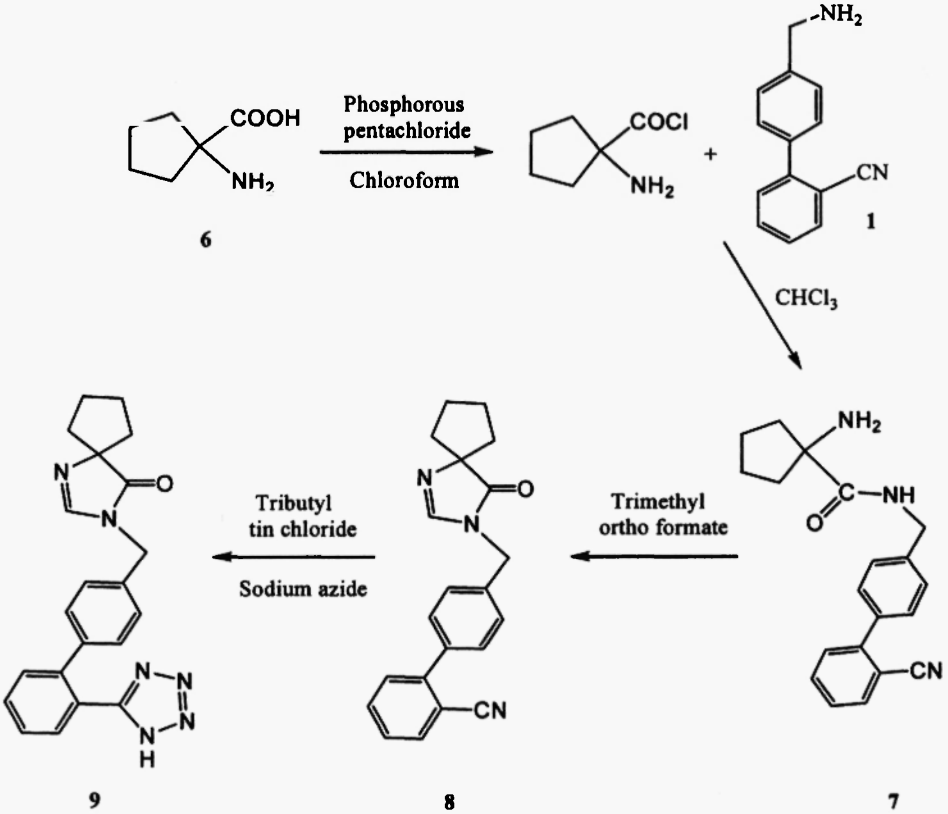
N-(2'-Cyano-biphenyl-4-ylmethyl)-2, 2, 2-trifluoro acetamide **4** on reaction with tributyl tin chloride and sodium azide in the presence of xylene resulted in 2, 2, 2-trifluoro-*N*-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-acetamide **5** (Scheme 2). The molecular ion of **5** appeared as the base peak at m/z 348 in the EI mass spectrum. It exhibited NH and C=O absorptions at 3297.7, 3033.1 and 1697.2 respectively. The methylene proton attached to the NH appeared as a singlet at 4.5-4.7 δ whereas the aromatic protons appeared as a multiplet at 7.4-7.8 δ.



Scheme-2

3-[2'-1H-Tetrazol-5-yl)-biphenyl-4-yl methyl]-1, 3-diaza-spiro [4, 4] non-1-en-4-one (9)

1-Amino-cyclopentanecarboxylic acid (4) **6** on reaction with phosohorous pentachloride gave a non-isolable acyl intermediate, which was further condensed with 2-(4-aminomethyl phenyl) benzonitrile **1** to yield 1-amino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **7**. Trimethyl ortho formate mediated cyclization of 1-amino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide **7** gave 4'-(4-oxo-1,3-diaza-spiro [4,4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile **8** which was further elaborated into a tetrazole moiety by reacting it with tributyl tinchloride and sodium azide in the presence of xylene solvent which furnished 3-[2'-1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro [4,4] non-1-en-4-one **9** (Scheme-3).



Scheme-3

Conclusion

Keeping in view the large-scale API production, its commercialization and the need for stringent purity requirements in regulated markets, it becomes compulsory to identify, characterize and synthesize the possible impurities. Hence, our efforts to synthesize and characterize the impurities of Irbesartan prove to be valuable.

Experimental Section

^{1}H NMR spectra were measured on a Gemini 200-MHz FTNMR Spectrometer and the chemical shifts were reported as δ values in ppm relative to TMS as an internal standard. The IR spectra were recorded in the solid state as KBR dispersion using Perkin Elmer FT-IR Spectrophotometer. Mass spectra were recorded on Shimadzu LCMS-QP 8000, LC-MS and AB-4000 Q-trap LC-MS/MS.

Pentanoic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (2)

To a solution of 4'-aminomethyl-biphenyl-2-carbonitrile (**1**, 20.0 g, 0.096 mol) in chloroform (40 mL), pentanoyl chloride (0.115 mol) was added slowly and was maintained at 25-35 ^{0}C for reaction completion. To the reaction mass, water (200 mL) was added. The organic and aqueous layers were separated and the organic layer was washed with saturated sodium bicarbonate solution followed by water. The organic layer was concentrated under reduced pressure, triturated with cyclohexane (100 mL) and recrystallized in toluene to yield **2** (Yield: 24.0 g, 85.6 %).

IR (cm^{-1}): 3300.9 (NH), 2224.1 (CN), 1645.6 (C=O)

^{1}H NMR ($CDCl_3$): 0.8-1.0 (t, 3H, CH_2), 1.3-1.5 (sext, 2H, CH_2), 1.6-1.8 (pent, 2H, CH_2), 2.2-2.4 (t, 2H, CH_2), 4.3-4.5 (s, 2H, CH_2), 7.3-7.9 (m, 8H, Ar-H)

Mass: 293 (M^+)

Anal. Calcd. for $C_{19}H_{20}N_2O$ (292.37): C, 78.05; H, 6.89; N, 9.58

Found: C, 78.34; H, 6.80; N, 9.69

Pentanoic acid (2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl)-amide (3)

A mixture of **2** (10.0 g, 0.0342 mol), xylene (20 mL), tributyl tin chloride (22.26 g, 0.0684 mol) and sodium azide (4.46 g, 0.0684 mol) was refluxed till reaction completion. The reaction mass was cooled to 25-35 ^{0}C, diluted with water (50 mL), followed by acetone (50 mL), stirred and acidified with acetic acid to pH ~4. The isolated solid was filtered, washed with cyclohexane (20 mL) and dried to a constant weight at 60-70 ^{0}C to yield **3** (Yield: 10.3 g, 90%).

IR (cm^{-1}): 3280.7 (NH), 3101.6 (NH), 1634.1 (C=O)

^{1}H NMR ($CDCl_3$): 0.8-1.0 (t, 3H, CH_2), 1.3-1.5 (sext, 2H, CH_2), 1.6-1.8 (pent, 2H, CH_2), 2.2-2.4 (t, 2H, CH_2), 4.5-4.7 (s, 2H, CH_2), 7.4-7.9 (m, 8H, Ar-H)

Mass: 336 (M^+)

Anal. Calcd. for $C_{19}H_{21}N_5O$ (335.40): C, 68.04; H, 6.31; N, 20.88

Found: C, 68.21; H, 6.28; N, 21.04

***N*-(2'-Cyano-biphenyl-4-ylmethyl)-2, 2, 2-trifluoro acetamide (4)**

A mixture of 4'-aminomethyl-biphenyl-2-carbonitrile (**1**, 10.0 g, 0.048 mol), dichloromethane (20 mL), dicyclohexyl carbodiimide (DCC) (9.9 g, 0.048) and 1-hydroxy benzotriazole (HOBT) (1.3 g, 0.095 mol) was stirred at 25-35 ^{0}C for reaction completion. The reaction mass was filtered and the dichloromethane layer was washed with saturated sodium bicarbonate solution. The organic layer was concentrated under reduced pressure to yield a residue of 4 (Yield: 12.0 g, 82 %).

IR (cm^{-1}): 3294.3 (NH), 2227.0 (CN), 1701.4 (C=O)

^{1}H NMR (CDCl$_3$): 4.5-4.7 (s, 2H, CH$_2$), 7.4-7.8 (m, 8H, Ar-H)

Mass: 305 (M$^+$)

Anal. Calcd. for $C_{16}H_{11}F_3N_2O$ (304.27): C, 63.16; H, 3.64; N, 9.21

Found: C, 63.29; H, 3.55; N, 9.45

2, 2, 2-Trifluoro-N-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-acetamide (5)

A mixture of 4 (10.0 g, 0.033 mol) xylene (20 mL), tributyl tin chloride (21.3 g, 0.0656 mol) and sodium azide (4.26 g, 0.0656 mol) was refluxed till reaction completion. The reaction mass was cooled to 25-35 ^{0}C, diluted with water (50 mL) followed by acetone (50 mL), stirred and acidified with acetic acid to pH ~4. The isolated solid was filtered, washed with cyclohexane (20 mL) and dried to a constant weight at 60-70 ^{0}C to yield **5** (10.2 g. 89.4%)

IR (cm^{-1}): 3297.7 (NH), 3033.1 (NH), 1697.2 (C=O)

^{1}H NMR (CDCl$_3$): 4.5-4.7 (s, 2H, CH$_2$), 7.4-7.8 (m, 8H, Ar-H)

Mass: 348 (M$^+$)

Anal. Calcd. for $C_{16}H_{12}F_3N_5O$ (347.29): C, 55.33; H, 3.48; N, 20.17

Found: C, 55.51; H, 3.36; N, 20.41

1-Amino-cyclopentanecarboxylic acid (2'-cyano-biphenyl-4-ylmethyl)-amide (7)

A mixture of 1-amino cyclopentane carboxylic acid 6 (10.0 g, 0.076 mol), phosphorous pentachloride (32.2 g, 0.154 mol) and chloroform (100 mL) was maintained for 1 hour at 55-60 ^{0}C. To the reaction mass (14.4 g, 0.068 mol) of 2-(4-aminomethyl phenyl) benzonitrile (**1**, 14.4 g, 0.068 mol) in chloroform (50 mL) was added slowly for 30-45 minutes and was maintained at 60 ^{0}C for reaction completion. The reaction mass was decomposed using ice and water, basified with caustic lye to pH ~9.0. The organic and aqueous layers were separated and the organic layer was concentrated under reduced pressure to yield an oily residue 7 (Yield: 20.3 g, 82.0 %).

IR (cm^{-1}): 3370.5 (NH), 2223.7 (CN), 1648.8 (C=O)

^{1}H NMR (CDCl$_3$): 1.6-2.1 (m, 8H, CH$_2$), 4.6-4.7 (s, 2H, CH$_2$), 7.0-7.6 (m, 8H, Ar-H)

Mass: 320 (M$^+$)

Anal. Calcd. for $C_{20}H_{21}N_3O$ (19.40): C, 75.21; H, 6.63; N, 13.61

Found: C, 75.43; H, 6.59; N, 13.66

4'-(4-Oxo-1, 3-diaza-spiro [4, 4] non-1-en-3-ylmethyl)-biphenyl-2-carbonitrile (8)

A mixture of 7 (10.0 g, 0.031), trimethyl orthoformate (100 mL) was maintained at 90-95 °C till reaction completion. The reaction mass was cooled to 25-35 °C and to it water (100 mL) was added. The compound was extracted into dichloromethane and was concentrated under reduced pressure to yield residue of **8** (Yield: 9.3 g, 90%).

IR (cm^{-1}): 2223.6 (CN), 1656.4 (C=O)

^1H NMR ($CDCl_3$): 1.6-2.4 (m, 8H, CH_2), 4.4-4.6 (s, 2H, CH_2), 7.3-7.8 (m, 8H, Ar-H), 8.0-8.2 (s, 1H, HC=N)

Mass: 330 (M^+)

Anal. Calcd. for $C_{21}H_{19}N_3O$ (329.40): C, 76.57; H, 5.81; N, 12.76

Found: C, 77.32; H, 5.75; N, 13.38

3-[2'-1*H*-Tetrazol-5-yl)-biphenyl-4-ylmethyl]-1, 3-diaza-spiro [4,4] non-1-en-4-one (9)

A mixture of 8 (8.0 g, 0.024 mol), xylene (16.0 mL), tributyl tin chloride (5.8 g, 0.0178 mol), sodium azide (3.1 g, 0.048 mol) was refluxed till reaction completion. The reaction mass was cooled to 25-35 °C, to it water (80.0 mL) was added and pH was adjusted to ~9.0. The organic and aqueous layers were separated and the aqueous layer pH was adjusted to 4.0 using acetic acid. The product was extracted into dichloromethane and was concentrated under reduced pressure. The solid compound was isolated using cyclohexane and recrystallized to yield 9 (Yield: 7.8 g, 86.3%).

IR (cm^{-1}): 3422.3 (NH), 1729.2 (C=O)

^1H NMR ($CDCl_3$): 1.7-2.0 (m, 8H, CH_3), 4.6-4.8 (s, 2H, CH_2), 7.1-7.2 (m, 2H, Ar-H), 7.2-7.3 (m, 2H, Ar-H), 7.5-7.6 (m, 2H, Ar-H), 7.6-7.7 (m, 2H, Ar-H), 7.9-8.0 (s, 1H, HC=N)

Mass: 373 (M^+)

Anal. Calcd. for $C_{21}H_{20}N_6O$ (329.40): C, 67.73; H, 5.41; N, 22.57

Found: C, 67.84; H, 5.35; N, 22.72

Acknowledgements

The authors wish to thank the management of Dr. Reddy's Laboratories Ltd., Bulk Actives Unit IV for supporting this work.

References

1. Claude, B.; Jean Claude, B.; Jacques, C.; Dino, N.; Pierre, P.; Claude, M.; Yvette, M. US Patent 5,270,317, December 14, (1993).
2. Communicated to *Heterocyclic Communications* on 24th January, (2006).
3. Takehiko N.; Kohei N.; Takeshi K. US Patent 6, 608, 210 B2; Chem. Abstr., 116, 1289124, 1992.
4. Bin Ho; Michael Crider A.; Stables James P. *J. Med. Chem.* 2001, 36, 265-286.

Received on January 27, 2007