Improved Green Method for Synthesis of Irbesartan, an Antihypertensive Drugs

Omvir Singh[1], Harish Kumar Chopra[2], Paikhomba Loktongbam[3]

[1,3] Student, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India
[2] Professor, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

Abstract- An improved green method for synthesis of the antihypertensive drug irbesartan, based on the Bromination by green method and Suzuki coupling reaction, has been described.

Index Terms- Antihypertensive drug, Irbesartan, synthesis

I. INTRODUCTION

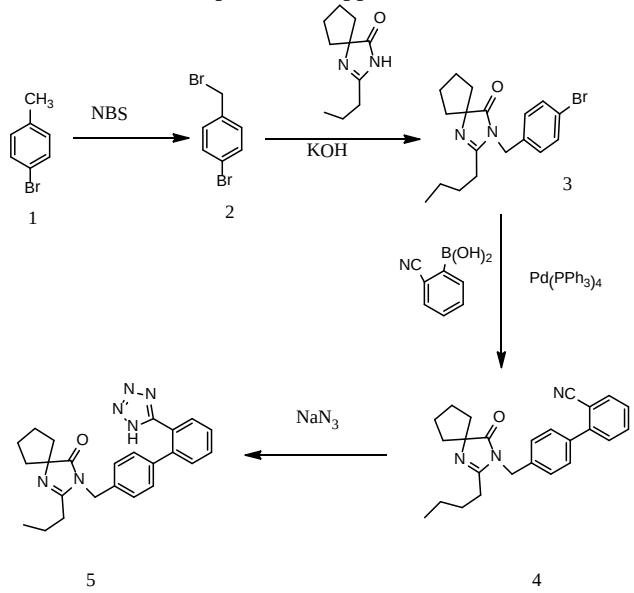
Hypertension is the serious medical condition which is mainly responsible for cardiovascular diseases. Renin-Angiotensin-Aldosterone System (RAAS) is the basic system in humans, which is used to regulate the blood pressure as well as the related values such as sodium levels. Targeting the Angiotensin1 (AT_1) receptors of Angiotensin-II with nonpeptide based drugs which are otherwise called as Angiotensin Receptor Blockers (ARB's), led to the control of hypertension, ultimately controlling its associated heart related ailments such as coronary heart disease and stroke. Irbesartan, is a non-peptide angiotensin II receptor antagonist used in the treatment of hypertension, heart strokes, diabetic neuropathy and congestive heart diseases. Irbesartan is currently available in the market as an antihypertensive drug under the brand name of Avapro. The metabolism of Irbesartan, a highly selective and potent nonpeptide angiotensin II receptor antagonist, has been investigated in humans. Irbesartan inhibits the activity of angiotensin II (AII) via specific, selective non-competitive antagonism of the AII receptor subtype 1 (AT1) which mediates most of the known physiological activities of AII. Our present work describes an improved green method for synthesis of Irbesartan.this paper is divided into four sections ,the first section deals with the discussion of the chemicals involved ,the second section deals with the experimental analysis ,the third gives the conclusion.

II. DISCUSSION

The reported synthetic approach starts with 4-Bromo toluene. The bromination of 4-Bromo toluene by green, efficient ultrasonic method to give 4-Bromo benzyl bromide. 4-Bromobenzyl bromide can subsequent condensation with 2-Butyl-1,3-diaza-Spiro [4.4] non-1-en-4-one and then the key intermediate efficiently catalysed the homogeneous catalyst the new Suzuki–Miyaura cross-coupling conditions to give the phenyl–phenyl bond. The final steps are tetrazole formed, formed from the organic nitriles and azide, to give irbesartan as a final product.

III. EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker Advance II 400 spectrophotometer using TMS as internal standard, and the chemical shifts were reported on d ppm relative to TMS.



Reaction scheme

1. 4-Bromobenzyl bromide (2)

The reaction was carried out under ultrasound waves by using a probe ultrasonicator. In a typical reaction 0.32 gm (3.0 mmol) of p-Bromo toluene (1) and 0.54 gm (3.0 mmol) of N-Bromo succinamide (NBS) in 15 ml of water were syndicated at 40 ℃ for 40 min. After that, hexane was added and the reaction mixture was cooled and poured into a separatory funnel. The organic layer was washed 3 times with 15 ml of water and the combined organic extract was dried over anhydrous sodium sulfate to get the white solid of 4-Bromobenzyl bromide (2,0.42gm,77.7%).The product was crystallized with ethanol [1]. ^{1}H NMR ($CDCl_3$): δ=7.82-7.86(d,2H), 7.05-7.12(d,2H),4.30-4.56(s,2H).

2. 3-[4-Bromobenzyl]-2-butyl-1,3-diazo Spiro [4,4] non-1-en-4-one (3)

A mixture of N, N-dimetyl formamide (DMF) 9.36 ml, 2-n-butyl-1,3-diazo Spiro [4,4] -non-1-ene hydrochloride (1.97 gm, 0.36 mol) and potassium hydroxide (1.33 gm, 1 mol) was stirred at room temperature for 30-40 min. After that, a solution of 4-bromobenzyl bromide (2.38 gm, 0.4 mol) in DMF was added

dropwise, into the reaction mixture. The reaction was stirred at room temperature for 18 hours. After completion of the reaction, 100 ml of water was added over a period of 30 min and extracted with n-heptane (25 ml). The organic layer was washed with water, dried, and concentrated under reduced pressure to get the product [2]. The product (3, 2.12g, 90.6%), which was used in the next stage.

^{1}H NMR ($CDC1_3$): 0.7–0.9 (t, 3H, CH_3), 1.1–1.4 (sextet, 2H, CH_2), 1.4–1.6 (quintet, 2H, CH_2), 1.6–2.0 (m, 8H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.4–4.6 (s, 2H, Ar–CH_2), 6.8–7.0 (d, 2H, Ar–H), 7.3–7.5 (d, 2H, Ar–H).

3. 2-n-butyl-3-[(2-cyano biphenyl-4-yl) methyl] 1,3-diazo Spiro [4,4] non-1-en-4-one(4)

A 50 ml round bottom flask was charged with Pd (PPh_3) (3.46 gm, 0.3 mmol), benzene (10 ml), 3-[4-bromobenzyl]-1, 3-diazo Spiro [4, 4] non-1-en-4-one (3.64 gm, 10 mmol) and 10 ml aqueous solution of sodium carbonate (2 M) under nitrogen atmosphere. Next 2-cyano phenylboronic acid (1.616 gm, 11 mmol) in ethanol (5 ml) was added slowly with continuous stirring. Then, the mixture was refluxed for 8 hours. After the reaction completion, H_2O_2 (0.5 ml) was added and the mixture was stirred for 1 hour to oxidize the remaining phenylboronic acid. The product was extracted with ether, washed with saturated NaCl solution and then dried over anhydrous sodium sulfateto obtained yellow liquid of 2-n-butyl-3-[(2-cyano biphenyl-4-yl) methyl] 1,3-diazo Spiro [4,4] non-1-en-4-one**(**4 ,2.52gm,71%) [3].

^{1}H NMR ($CDCl_3$): δ=0.7(t,3H), 1.3(sextet,2H), 1.5(quintet,2H), 1.7(m,8H), 2.3(t,2H), 4.7(s,2H), 7.0-7.8(m,8H).

4. 2-Butyl-3-[[2-(1H-tetrazol-5-yl)[1,1^0-biphenyl]-4-yl]methyl]-1,3diazo Spiro[4,4] non-1-en-4-one (5)

A mixture of 2-n-butyl-3-[(2-cyano biphenyl-4-yl) methyl] 1,3-diazo Spiro [4,4] non-1-en-4-one (734mg, 2.0 mmol) and sodium azide (65mg, 3.0 mmol) in DMF (5ml), iodine (0.03mg) was stirred at 120 °C for 10 hours. After completion of the reaction, the mixture was treated with ethyl acetate (30 ml) and 4M HCl (20 ml) and stirred vigorously, The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2*10ml) [4] .The combined organic portion was washed with a saturated sodium thiosulfate solution (2*10ml) and water (2*10ml)[i].Recrystallization using methyl isobutyl ketone afforded butyl-3-[[2-(1H-tetrazol-5-yl) [1,1-biphenyl]-4 yl]methyl]1,3-diazo spiro [4,4] non-1-en-4-one , (5,595mg, 81%) as a yellow solid.

^{1}HNMR ($CDCl_3$): δ==0.7(t,3H), 1.3(sextet,2H), 1.5(quintet,2H), 1.7(m,8H), 2.3(t,2H), 3.0-3.6(s,1H), 4.7(s,2H), 7.0-7.8(m,8H).

IV. CONCLUSION

Many methods are available for preparation of Irbesartan drugs (for antihypertensive drugs) in the market, however there is a need to develop an ideal commercial process, which should be safe, ecologically sound, economically viable and meets the required quality specifications. This experiment aims to achieve an advanced technique, which is still not reported yet in the research world.

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AUTHORS

First Author – Omvir Singh, Student, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India, omvir10011995@gmail.com

Second Author – Harish Kumar Chopra, Professor, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

Third Author – Paikhomba Loktongbam , Student, Sant Longowal Institute of Engineering and Technology, Sangrur, Punjab, India

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