An efficient and green synthetic route to losartan

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A practical, efficient and green process for the preparation of losartan, an antihypertensive drug, has been developed with an overall yield of 58.6%. The key step is the synthesis of the two key intermediates 2-butyl-4-chloro-3*H*-imidazole-5-carbaldehyde (BCFI) and 2-cyano-4'-methyl biphenyl (OTBN). BCFI was synthesised from valeronitrile and acetyl chloride by three steps with an overall yield of 69%; OTBN was obtained in 86% yield by the coupling of *o*-chlorobenzonitrile with *p*-methylphenylmagnesium chloride in tetrahydrofuran in the presence of manganese chloride and chlorotrimethylsilane. The above route was successfully operated in at a pilot-plant operation.

Keywords: o-chlorobenzonitrile, p-methylphenylmagnesium chloride, losartan, manganese chloride, chlorotrimethylsilane, green synthesis

The rennin–angiotensin system has an important role in the maintenance of blood pressure and cardiovascular regulation.¹ Angiotensin II is the principal active hormone of this system and acts through the stimulation of specific receptors located in various organs.^{2,3} Angiotensin II antagonists are medicines that can be used in the treatment of hypertension, anxiety, glaucoma, and cardiac events.⁴ Among cardiovascular drugs, angiotensin II receptor antagonists such as losartan potassium have been widely used as an active ingredient in the management of hypertension. Furthermore, losartan **8** also plays an effective role in patients with an intolerance to ACE inhibitors.

In 1990, a group of Abbott scientists initiated an angiotensin II project using the DuPont⁵ angiotensin II antagonist as the starting point. In 1995, Losartan was the first non-peptide angiotensin II receptor blockers that could be easily accepted by patients safely and effectively.⁶ It has already been approved by the US Food and Drug Administration for clinical use.⁷ Losartan has been considered to be an ideal drug for treatment of hypertension and congestive heart failure that has good market prospects due to its fewer side effects, better drug action, long action time and ease of use.⁸⁻¹⁰

In particular, losartan has been approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Reports are available regarding the various routes, methodologies, and processes that have been adopted. These processes have restricted application in industry because of low overall yield,11 cumbersome workup process,12,13 difficult workup, and recovery of excessive organotin reagent.14 A recently developed process¹⁵ for losartan used sodium azide and triethylamine hydrochloride salt to construct a tetrazole ring from the cyano group. However, this process suffers from disadvantages such as treatment with hydrochloric acid which incurs safety concerns as it generates hydrazoic acid from the unreacted sodium azide in the reaction mixture. Hydrazoic acid is toxic and extremely explosive.16 To minimise the cost constraint and the number of steps, we avoided the use of tributyltin azide and replaced tributyltin azide or triethylamine hydrochloride salt¹⁷ with sodium azide and zinc trifluoromethanesulfonate. For the synthesis of the important intermediate 2-butyl-4-chloro-1H-imidazole-5-carbaldehyde, we started from valeronitrile and methanol in the presence of acetyl chloride. This new approach avoids the environmental pollution from hydrogen chloride gas and permits the easy control of the reaction conditions.

In view of the high volume requirement, large costs associated with this molecule, and disadvantages from the reported processes, there arises a need to develop a safe process for losartan to meet with all regulatory aspects. We now report a practical and efficient synthetic route to losartan which has been established in our laboratory and the corresponding pharmaceutical factory as shown in Fig. 1.



Fig. 1 Synthetic route for drug losartan.

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Results and discussion

Synthesis of 2-cyano-4'-methyl biphenyl

The synthesis of 2-cyano-4'-methyl biphenyl (OTBN) started from the commercially available p-chlorotoluene by the coupling of o-chlorobenzonitrile with p-methylphenylmagnesium chloride in tetrahydrofuran in the presence of manganese chloride and chlorotrimethylsilane. In the first set of the experiments, we evaluated the influence of the amount of the catalysts on the reaction. As shown in Table 1, when the amount of manganese chloride was less than 10% and the amount of chlorotrimethylsilane was constant, the yield was positively related to the amount of manganese chloride. When the amount of manganese chloride was more than 10%, the yield decreased. The function of manganese chloride was to protect the cyano group. However, adding too much manganese chloride resulted in the homo-coupling of the p-methylphenylmagnesium chloride. In this context, 0.1 equiv. of manganese chloride was the most appropriate.

Next, we investigated the influence of different molar ratio of p-methylphenylmagnesium chloride and o-chlorobenzonitrile on the yields of the products (Table 2). It appeared that with the increase in the proportion of p-methylphenylmagnesium chloride to o-chlorobenzonitrile, the yield increased until the ratio reached 3:1. On further increasing the amount of p-methylphenylmagnesium chloride, the yield exhibited a significant decrease. Meanwhile, the homo-coupled product from p-methylphenylmagnesium chloride increased. Based on above results, a ratio of 1.5:1 p-methylphenylmagnesium chloride/o-chlorobenzonitrile was best for this reaction. Using this method, we have managed to improve the yields significantly in comparison with previously published work. Under the optimum synthetic conditions, the yield of OTBN is up to 86.1%.

Table 1 Effect of catalyst on the yield of OTBN

MnCl ₂ /mol%	(CH ₃) ₃ SiCl/mol%	Yield/%ª	
5.0	5.0	58.8	
5.0	10.0	66.0	
5.0	20.0	79.4	
10.0	5.0	75.3	
10.0	10.0	89.1	
10.0	20.0	91.5	
20.0	5.0	72.2	
20.0	10.0	10.0 83.6	

^alsolated yield based on the o-chlorobenzonitrile

 Table 2 Effect on the yield of different molar ratio of the reactants

<i>p</i> -Methylphenylmagnesium chloride ^a / <i>o</i> -chlorobenzonitrile	Yield/% ^b
1.05:1	75.7
1.2:1	78.9
1.5:1	86.1
1.7:1	88.7
2.0:1	89.1
2.5:1	91.0
3.0:1	92.3
3.4:1	78.5
3.8:1	70.7
5.5:1	50.8

^a Obtained by calculating the amount of the magnesium.

^b Isolated yield based on the *o*-chlorobenzonitrile.

Synthesis of 2-butyl-4-chloro-3H-imidazole-5-carbaldehyde

Most of the processes which have been developed for the synthesis of another important intermediate, 2-butyl-4chloro-3*H*-imidazole-5-carbaldehyde (**5**), hydrogen chloride gas and ammonia were used under high pressure. These processes have restricted application in the industry because of environmental pollution and harsh reaction conditions. Our strategy for the synthesis of **5** is shown in Fig 1. We started from the commercially available valeronitrile and methanol in the presence of acetyl chloride under the conditions of $0-5^{\circ}$ C and atmospheric pressure. This process is easy to control and can avoid environmental pollution from hydrogen chloride gas and ammonia.

Synthesis of tetrazole

The construction of the tetrazole ring was accomplished by mixing of **7**, sodium azide and zinc trifluoromethanesulfonate in water. The tetrazole formation reaction proceeded smoothly in a short period (6 h), when 0.5 mmol **7** and 1.25 mmol sodium azide were utilised under 100°C, losartan is formed (91.0%). This process can avoid the environmental pollution caused by organic solvents and dramatically shorten the rection time under low reaction temperature. We have tried to evaluate the influence of time and solvent on the yield (Table 3).

As Table 3 shows, four solvents were tried (entries 1 to 4) at their boiling point. Analysing the yield of product; it was found that water as a solvent gave a higher yield at 100°C. From solvents 4 to 7, the influence of time and temperature on the yield is discussed in the solvent of DMF; the results show that the yield was reduced as the temperature is reduced. In conclusion, at 100°C, a reaction of 6 h in water gave a higher yield (91.0%). This avoided the environmental pollution caused by organic solvents.

Conclusion

In summary, a practical and efficient process for the preparation of losartan **8**, an antihypertensive drug, has been developed with an overall yield of 59%. This process involves a convergent combination of two key intermediates 2-butyl-4-chloro-3*H*imidazole-5-carbaldehyde and 2-cyano-4'-methylbiphenyl, which can be prepared from valeronitrile and acetyl chloride by three steps with an overall yield of 69% and from the coupling of *o*-chlorobenzonitrile with *p*-methylphenylmagnesium chloride respectively. A pilot-scale operation has also been demonstrated.

In the case of the synthetic method of losartan, a new synthetic route has been designed to overcome the shortcomings in the process of the protection and deprotection of triphenyl group. The participation of hydrogen chloride and ammonia is

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No.	Solvent	Time/h	Temperature/ºC	Yield/%
1	<i>p</i> -Xylene	24	140	0
2	DMSO	24	189	52.3
3	H ₂ 0	24	100	91.0
4	DMF	24	153	88.5
5	DMF	24	100	75.3
6	DMF	10	100	52.8
7	DMF	6	100	50.6
8	H ₂ 0	10	100	91.0
9	H,0	6	100	91.0
10	H ₂ 0	5	100	87.5

avoided. This new synthetic route of losartan is important, as a novel design route, using cheap raw materials, and convenient workup.

Experimental

All chemicals were purchased from J&k Chemical, Energy Chemical and Sinopharm. All the solvents were of analytical grade and used without further purification. TLC was used to check the purity of the as-synthesised compounds. NMR spectra were recorded on a Varian INOVA-400 MHz spectrometer. HRMS were recorded on MAT 95 XP produced by the Thermo Finnigan Company. Thermal analysis was carried out on XT-4 binocular microscope melting point apparatus, .

2-Cyano-4'-methylbiphenyl (2): A 1000 mL bottle containing o-chlorobenzonitrile (137.6 g, 1.0 mol), anhydrous manganese chloride (12.6 g, 0.1 mol), and chlorotrimethylsilane (10.8 g, 0.1 mol) was stirred at -5-0°C in anhydrous THF (200 mL) under nitrogen, and the prepared p-methylphenylmagnesium chloride was added over 1 h. The mixture was stirred at 25°C for 8 h and poured into concentrated hydrochloric acid to bring the pH of the solution close to 2. The mixture was extracted with ethyl acetate. The organic phase was washed with water, and dried over anhydrous MgSO₄. The solvent was removed at reduced pressure. The resulting residue was purified by silica gel column chromatography to provide 2-cyano-4'-methylbiphenyl (2) as a white solid (166.3 g, 86%). We have investigated the influence of different molar ratio of p-methylphenylmagnesium chloride/o-chlorobenzonitrile and the amount of catalysts on the yield. The results are shown in Tables 1 and 2. M.p. 47–48 °C(lit.¹⁸ 49 °C) ¹H NMR (400 MHz, CDCl₂) δ 7.76 (d, J = 7.7 Hz, 1H), 7.63 (td, J = 7.7, 1.3 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.42 (td, J = 7.7, 1.2 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 21.2, 111.2, 118.8, 127.2, 128.6, 129.4, 129.9, 132.7, 133.7, 135.2, 138.7, 145.4. HRMS calcd for C₁₄H₁₁N 193.0891, found 193.0889.

2-*Cyano-4'-bromomethylbiphenyl* (**3**): 2-Cyano-4'-methylbiphenyl (0.193 g, 1 mmol) was added to a solution containing CCl_4 (5 mL, 0.196 g) *N*-bromosuccinimide (NBS, 1.1 mmol) and azobisisobutyronitrile (AIBN0.017 g, 0.1 mmol) in a two-necked flask equipped with a condenser, and then the solution was kept at 80°C for 3 h. The mixture was cooled to room temperature and it was diluted with ethyl acetate (10 mL) and washed twice with water (2×10 mL), dried over anhydrous MgSO₄ and evaporated. The residue was purified by silica gel column chromatography to give 2-cyano-4'-bromomethylbiphenyl (**3**) as a white solid (0.249g, 91%); m.p. 120–122°C (lit.¹⁹ 114.5–120°C) ¹H NMR (400 MHz, CDCl3) δ 7.70 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.59 (td, *J* = 7.7, 1.3 Hz, 1H), 7.50–7.42 (m, 5H), 7.39 (td, *J* = 7.7, 1.2 Hz, 1H), 4.48 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 143.7, 137.3, 137.2, 132.8, 131.9, 129.0, 128.4, 128.2, 126.8, 117.6, 110.2, 31.8. HRMS calcd for C₁₄H₁₀NBr 270.9997, found 270.9991.

2-Butyl-4-chloro-1H-imidazole-5-carbaldehyde (5): Valeronitrile (0.83 g, 10 mmol) and methanol (4 g) were added to the flask, then acetyl chloride (1.18 g, 15 mmol) was added dropwise at 0 °C. After 2 h, the valeronitrile was completely reacted. The mixture was to pH = 9 by adding sodium hydroxide solution. The aqueous phase was extracted with toluene and the organic phases were combined. Then, methanol (4 g), sodium methoxide (0.030 g), glycine (0.825 g) were added and the resulting solution was stirred at 0°C for 2 h. After filtration of the mixture, the resulting white solid was washed with cold toluene and dried under reduced pressure at 40-50°C to give N-carboxymethyl pentamidine. Then, POCl₃ (0.431 g, 2.8 mmol) and DMF (0.219 g, 3 mmol) was added dropwise to a flask containing N-carboxymethyl pentamidine (0.158 g, 1 mmol) and toluene (5 mL). The temperature was maintained below 60°C. After the addition, the reaction mixture was heated to 100°C for 2 h. Then the solution was cooled, and some cool distilled water and sodium hydroxide solution was added to adjust the pH to 2. The solution was washed with toluene (20 mL) and the organic phase was combined. Then the solution was evaporated about 50% and cooled to 0 °C. The crystallised solid was filtered, washed with cold toluene and dried under reduced pressure at 40–50°C to give 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde (**5**) (0.154 g, 82%); m.p. 92–93°C (lit.²⁰ 93°C) ¹H NMR (400 MHz, CDCl₃) δ 11.48 (s, 1H), 9.55 (s, 1H), 3.02–2.43 (m, 2H), 1.70 (d, *J* = 15.3 Hz, 2H), 1.41–1.22 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 177.7, 154.9, 142.0, 125.8, 29.8, 28.6, 22.2, 13.6. HRMS calcd for C₁₄H₁₀ON₃Cl 186.0560, found 186.0553.

2-Butyl-4-chloro-5-hydroxymethyl-1-{[(2'-cyano)-[1,1'-biphenyl]-4-yl]-methyl]-1H-imidazole (7): 2-Butyl-4-chloro-1H-imidazole-5carbaldehyde (0.185g, 1 mmol) and potassium carbonate (0.230 g, 1.67 mmol) was added to a solution of 2-cyano-4'-bromomethylbiphenyl (0.299 g, 1.1 mmol) in DMF (5 mL) at room temperature. The resulting mixture was heated to 40°C for 6 h. After completion of the reaction, methanol (1.5 g) was added followed by slow, dropwise addition of sodium borohydride (0.023 g) over 10 min while the temperature was maintained at room temperature. After completion of the addition, the mixture was stirred at 40°C for 1 h. Distilled water was added to quench the excess sodium borohydride, and the resultant mixture was stirred for 20 min. The precipitated solid was filtered, washed with water (2×10 mL) and toluene (2×10 mL) to give 2-butyl-4-chloro-5-hydroxymethyl-1-{[(2'-cyano)-[1,1'-biphenyl]-4-yl]-methyl}-1Himidazole (7) (0.369 g, 93%); m.p. 158–159°C (lit.¹⁷ 159–160°C) ¹H NMR (400 MHz, CDCl₂) δ 7.70 (d, J = 7.7 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 13.7 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 5.22 (d, J = 10.8 Hz, 2H), 4.45 (d, J = 9.2 Hz, 2H), 2.59–2.46 (m, 2H), 1.67–1.50 (m, 2H), 1.25 (q, J = 13.8 Hz, 2H), 0.81 (t, J = 7.3 Hz, 3H).¹³C NMR (101 MHz, CDCl₃) δ 147.7, 132.8, 131.9, 128.9, 128.4, 126.8, 125.2, 117.5, 110.2, 52.2, 46.2, 28.7, 25.7, 21.4, 12.7. HRMS calcd for C₂₂H₂₂ON₃Cl 379.1451, found 379.1432.

Losartan (8): Sodium azide (82 mg, 1.25 mmol) and zinc trifluomethanesulfonate was added to a solution of 2-butyl-4-chloro-5-hydroxymethyl-1-{[(2'-cyano)-[1,1'-biphenyl]-4-yl]-methyl}-1H-imidazole (7) (0.190 g, 0.5 mmol) in water at room temperature. The resultant mixture was heated to 100°C and maintained at this temperature for 6 h. The resulting precipitated solid was filtered and washed with water. The crude product was dissolved in acetone at room temperature and then heated under reflux for 1 h, and then cooled to room temperature. The resultant reaction mixture was stirred at room temperature for 2h, during which a crystalline solid was formed. The crystals were filtered, washed with acetone, and dried under vacuum at 50-60°C to afford 0.192 g (91%) of the title compound losartan (8); m.p. 183.5–184.5°C (lit.¹⁷ 184.3–186°C) ¹H NMR (400 MHz, DMSO) δ 7.95 (d, J = 7.6 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 7.65–7.51 (m, 4H), 7.24 (d, J = 8.1 Hz, 2H), 5.35 (s, 2H), 5.28 (t, J = 5.2 Hz, 1H), 4.37 (d, J = 5.2 Hz, 2H), 3.34 (s, 2H), 1.56-1.37(m, 2H), 1.33-1.14 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H). HRMS calcd for C₂₂H₂₃ON₆Cl 422.1622, found 422.1718.

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