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New Strategy for the Synthesis of Telmisartan: An Antihypertensive Drug

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An improved, convergent and industrially useful process suitable for large-scale production of telmisartan has been described. The key steps are Suzuki coupling for the preparation of key intermediate 4,4-dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)oxazoline of telmisartan, N-alkylation and oxazoline hydrolysis.

Key Words: Telmisartan, Antihypertensive drug, Suzuki coupling and Oxazoline hydrolysis.

INTRODUCTION

Telmisartan (**1**) (Fig. 1) is an angiotensin II receptor antagonist useful in the treatment of hypertension, heart diseases, heart strokes and bladder diseases[1]. Telmisartan is currently available in the market as an antihypertensive drug[2] under the brand name of MICARDIS.

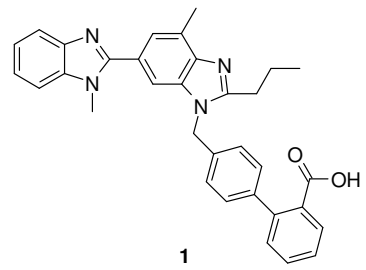

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Fig. 1. Telmisartan

The reported synthesis[3-5] of telmisartan in (**Scheme-I**) involves condensation of 7-methyl-2-propyl-3*H*-benzimidazole-5-carboxylic acid derivative (**2**) with diamine

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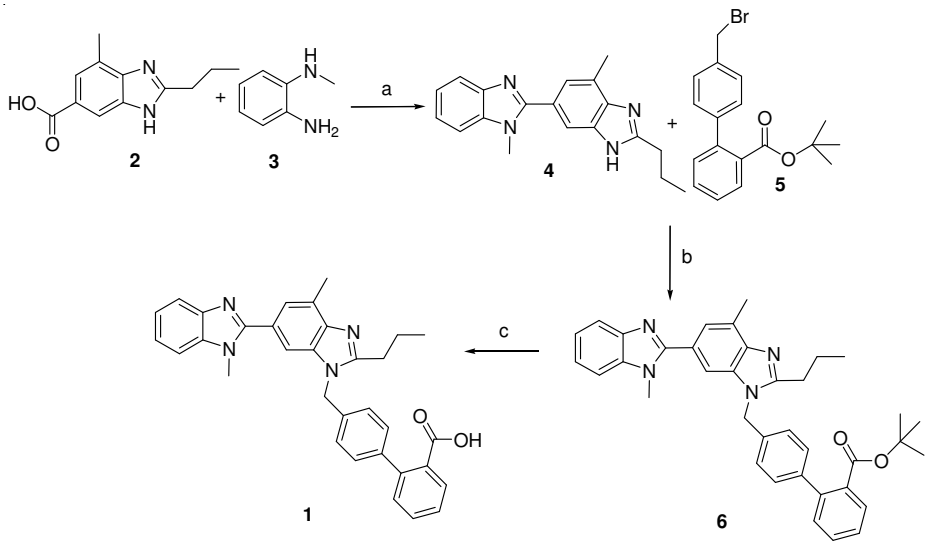
derivative N-methylbenzene-1,2-diamine (**3**) to get the dibenzimidazole derivative (**4**). Alkylation of compound **4** with 4'-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester (**5**) furnished ester derivative of telmisartan **6**. Ester hydrolysis of **6** in trifluoroacetic acid yielded telmisartan **1** in an overall yield of around 21 % with several impurities. This process suffers from disadvantages such as (a) linear multi step synthesis (b) poor stability of 4'-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester[6] **5** (c) low yield and purity obtained during the preparation of 4'-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester **5** due to the formation of 20-45 % of dibromo impurity **7** in bromination step (d) the solvents, dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) used in the penultimate stage are unrecoverable, while the use of potassium *tert*-butoxide resulted in the contamination of high organic volatile impurities (OVI) in telmisartan (e) deprotection of the *tert*-butyl group using trifluoroacetic acid in DMF lead to the formation of several byproducts (e) sulfated ash (*Residue on ignition*) in API (active pharmaceutical ingredient) obtained from this process is always more than 1.0 % which was not acceptable as per ICH (International Conference on Harmonisation) guidelines.



Scheme-I. Reagents and conditions: (a) Polyphosphoric acid, 150-155 °C, 4.0 h, 80 %; (b) KOt-Bu, dimethyl acetamide, 75-80 ºC, 3.0 h, 70 %; (c) Trifluoroacetic acid, DMF, 4.0 h, 70 %

In the present communication, we report the use of 4,4-dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)oxazoline[7] (**12**) instead of 4'-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester (5), which has an excellent shelf life (**Scheme-III**). This has provided advantage in improving the yield (overall yield: 75 %) of biaryl oxazoline intermediate in three steps and has also circumvented repeated column chromatograhic purification procedures.

EXPERIMENTAL

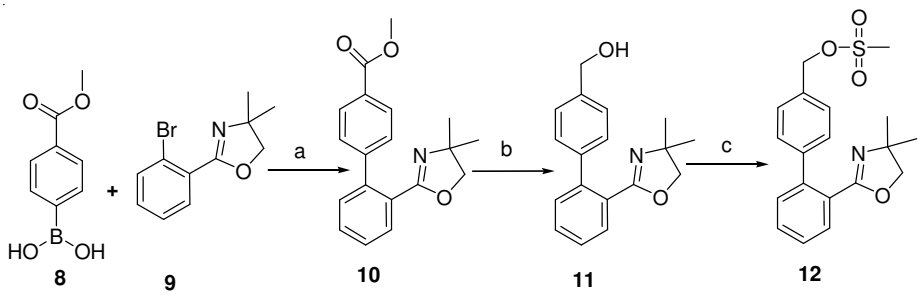
All solvents and reagents were purchased from the commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin layer chromatography was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS (Tetra methyl silane). The IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

2'-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carboxylic acid methyl ester (10): To a mixture of 4-(methoxycarbonyl)benzene boronic acid (**8**) (5.0 g, 0.027 mol) and 2-(2-bromophenyl)-4, 4-dimethyl-2-oxazoline (**9**) (7.76 g, 0.030 mol) in tetrahydrafuran (50.0 mL), 2 M aqueous sodium carbonate solution (20.0 mL) was added at room temperature. The resulting bi phasic solution was degassed with nitrogen gas for 20 min. *Tetrakis* triphenyl phosphine palladium (0) (0.25 g) was added and heated to reflux (64 ºC). The reaction mixture was maintained under reflux for 12 h. After completion of the reaction, the reaction mixture was cooled to 26 ºC and to this was added 50 mL of saturated ammonium chloride solution and 50 mL of ethyl acetate. Separated organic layer was washed twice with water (50 mL). Separated organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate 80:20 to get the title compound **10** as an oil (6.86 g, 80 %); ^{1}H NMR ($CDCl_3$) (δ ppm): 7.96 (d, 2H, ArH, J = 8.4 Hz), 7.66 (m, 1H, ArH, J = 7.4 Hz), 7.56 (m, 1H, ArH, J = 7.4 Hz), 7.48-7.44 (m, 2H, ArH), 7.42 (d, 2H, ArH, J = 8.4 Hz), 3.84 (s, 3H, -CH_3), 3.76 (s, 2H, -CH_2), 1.15 (s, 6H, 2x-CH_3); ^{13}C NMR ($CDCl_3$) (δ ppm); 24.6, 47.4, 62.8, 74.7, 123.0, 123.1, 123.6, 124.0, 124.5, 125.2, 125.5, 125.8, 135.8, 141.1, 158.3, 162.3; MS (m/z): 310 [M^+ + 1]; Anal. Calcd for $C_{19}H_{19}NO_3$ (309): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.56; H, 6.23; N, 4.59.

[2'-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methanol (11): To a mixture of 2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carboxylic acid methyl ester **10** (5.0 g, 0.016 mol) in THF and ethanol 1:1 mixture (20.0 mL), sodium borohydride (1.2 g, 0.032 mol) was added portion wise at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was cooled to 5-10 ºC and poured into a solution of saturated aqueous ammonium chloride (30 mL). To this was added of ethyl acetate (25 mL), separated organic layer and washed twice with water 20 mL. Organic layer was dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate 50:50 to get the

title compound **11** as a white solid (4.0 g, 90 %); melting point: 98-100 ºC (L^5 m.p. 97-100 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.74 (1H, m, *J* = 7.4 Hz, ArH), 7.49 (1H, m, *J* = 7.4 Hz, ArH), 7.40-7.39 (2H, m, ArH), 7.38 (2H, d, *J* = 8.0 Hz, ArH), 7.35 (2H, d, *J* = 8.0 Hz, ArH), 4.75 (2H, s, -CH_2), 3.80 (2H, s, -CH_2), 1.30 (6H, s, 2x-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 28.6, 64.3, 68.1, 78.9, 127.1, 126.9, 127.7, 128.5,129.4, 129.4, 130.2, 137.2, 140.2, 141.2, 164.9; MS (m/z): 282 [M^+ + 1]; Anal. Calcd. (%) for $C_{18}H_{19}NO_2$ (281): C, 76.84; H, 6.81; N, 4.98; Found: C, 77.02; H, 6.81; N, 4.90.

4,4-Dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)oxazoline (12): To a solution of [2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]-methanol (**11**) (4.0 g, 0.014 mol) in methylene chloride (40.0 mL), was added triethyl amine (2.8 g, 0.028 mol) followed by methane sulphonyl chloride (1.9 g, 0.017 mol) drop wisely at 0-5 ºC and maintained for 2 h. The reaction mixture was poured into an aqueous solution of 20 % of sodium hydrogen carbonate solution (40 mL). Separated the organic layer was washed twice with water (50 mL). The organic layer was concentrated under pressure to get the title compound **12** as an oil (**Scheme-II**) (5.0 g, 99 % yield); HRMS m/z calculated for $C_{19}H_{21}NO_4S$-359.1191 [M + 1], found -359.1183; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.82-7.15 (8H, m, ArH), 4.84 (2H, s, -CH_2), 3.81 (2H, s, -CH_2), 2.94 (3H, s, -CH_3), 1.29 (6H, s, 2x-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm); 28.6, 38.1, 68.1, 71.9, 78.9, 127.1, 127.4, 127.5, 127.7, 129.4, 129.6, 130.2, 135.2, 137.2, 140.2, 164.9.



Scheme-II. Reagents and conditions: (a) $Pd(PPh_3)_4$, aq. Na_2CO_3, THF, 12.0 h, 80 %; (b) $NaBH_4$, ethanol, THF, 3.0 h, 90 %; (c) CH_3SO_2Cl, TEA, DCM, 2.0 h, 99 %

3'-{[2'-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methyl}-1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzimidazole (13): A solution of 1,4'-dimethyl-2'-propyl-1*H*, 3'*H*-2,5-dibenzimidazole **4**, (3.0 g, 0.0098 mol), THF (30 mL) was added dropwise to the mixture of 60 % sodium hydride (0.59 g, 0.0148 mol) in THF (30 mL) under inert atmosphere. The reaction mixture was stirred for 0.5 h at room temperature. 4,4-dimethyl-2-(4'-methanesulfonyloxymethyl-biphenyl-2-yl)oxazoline (**12**) (4.2 g, 0.011 mol) in THF (30 mL) and dimethyl acetamide (10 mL) was added to the reaction mixture. Heated the reaction mixture to reflux and maintained for 8 h. After cooling the reaction mixture to 25-35 ºC, this was poured into

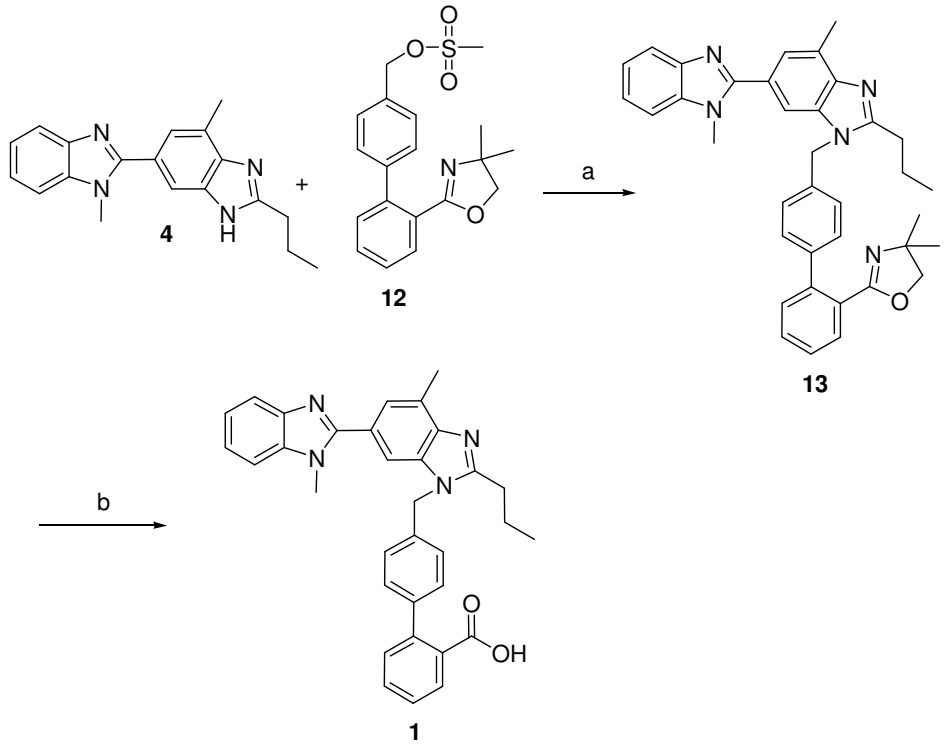
a solution of saturated aqueous ammonium chloride (50 mL). Product was extracted twice with ethyl acetate (50 mL) and evaporated under vacuum at 55 ºC. The obtained residue was triturated with *n*-hexane (36 mL) to get the solid material and filtered, dried at 50-55 °C for 3-4 h to obtain **13** as a white crystalline powder (yield 4.7 g, 85 % yield); melting point 191-193 °C; IR (KBr, cm^{-1}) 1630 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.78 (1H, d, *J* = 8.0 Hz, ArH), 7.68 (1H, m, *J* = 8.0 Hz, ArH), 7.47-7.26 (10H, m, ArH), 7.07 (2H, m, *J* = 8.0 Hz, ArH), 5.45 (2H, s, -CH_2), 3.82 (3H, s, -CH_3), 3.58 (2H, s, -CH_2), 2.97 (2H, t, *J* = 7.6 Hz, -CH_2), 2.74 (3H, s, -CH_3), 1.92 (2H, m , *J* = 7.6 Hz, -CH_2), 1.29 (6H, s, 2x-CH_3), 1.04 (3H, t, *J* = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 13.9, 16.7, 21.6, 27.6, 29.6, 31.6, 46.9, 67.2, 79.0, 108.8, 109.2, 119.3, 122.1, 122.2, 123.5, 123.6, 125.6, 127.0, 127.2, 128.8, 129.1, 129.7, 129.9, 130.2, 134.4, 134.8, 136.4, 140.6, 140.8, 142.6, 142.8, 154.2, 156.2, 163.1; MS (m/z): 568 [M^+ + 1]; Anal. Calcd for $C_{37}H_{37}N_5O$: C, 78.28; H, 6.57; N, 12.34. Found: C, 78.26; H, 6.56; N, 12.30.

4'-[(1,7'-Dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzimidazol-3'-yl)methyl] biphenyl-2-carboxylic acid (1): A mixture of **13** (4.0 g, 0.007 mol), concentrated hydrochloric acid (40.0 mL) was heated to reflux (100-105 ºC) for about 30 h. The reaction mass was cooled to 0-5 ºC. 20 % sodium hydroxide solution was added until the reaction mixture pH attained to 9-10 and further stirred at room temperature for 2 h. Desired solid was filtered and washed with water (50.0 mL). The wet cake was dissolved in a mixture of water (60.0 mL) and acetonitrile (20.0 mL) and then heated to 60-65 °C. The pH of the resulting clear solution was adjusted to 5.0-5.5 using 5 % acetic acid and stirring continued for 2 h. The precipitated solid was filtered and washed with water (50 mL). Dried at 70-75 °C for 4-5 h under a vacuum to obtain telmisartan **1** as a white crystalline powder (yield 3.0 g, 85 %); melting point: 260-262 °C (Lit.[8] m.p. 260-262 °C); IR (KBr, cm^{-1}) 2300-3500 (broad), 1680 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 12.8 (1H, s, -COOH), 8.42 (1H, d, *J* = 8.0 Hz, ArH), 8.02 (1H, d, *J* = 8.0 Hz, ArH), 7.50-7.26 (8H, m, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 7.05 (1H, s, ArH), 6.96 (1H, s, ArH), 5.42 (2H, s, -CH_2), 3.82 (3H, s, -CH_3), 2.97 (2H, t, *J* = 7.6 Hz, -CH_2), 2.74 (3H, s, -CH_3), 1.92 (2H, m, *J* = 7.6 Hz, -CH_2), 1.04 (3H, t, *J* = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm): 13.5, 16.7, 20.6, 27.6, 32.7, 47.1, 51.7, 112.0, 112.7, 114.7, 118.6, 125.3, 125.7, 125.8, 127.0, 127.4, 128.6, 129.3, 130.4, 130.6, 131.5, 132.3, 133.1, 133.2, 133.7, 134.5, 140.2, 140.5, 150.2, 157.3, 168.1; MS (m/z): 515 [M^+ + 1]; Anal. Calcd for $C_{33}H_{30}N_4O_2$: C, 77.02; H, 5.88; N, 10.89. Found: C, 77.0; H, 5.82; N, 10.86.

RESULTS AND DISCUSSION

In our attempts to prepare telmisartan **1**, we have developed an improved three-stage process employing Suzuki-coupling for the preparation of 4,4-dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)oxazoline (**12**). Subsequent condensation with dibenzimidazole derivative[4,5] **4** and acid hydrolysis of intermediate **13** provided telmisartan **1** in good yield.

We have identified 4-(methoxycarbonyl)benzene boronic acid (**8**) and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline[8] (**9**) as key starting materials for the preparation of key intermediate 4,4-dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)-oxazoline (**12**). Suzuki coupling was accomplished for the preparation of intermediate, 2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carboxylicacid methyl ester (**10**) by reacting 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline with 4-(methoxycarbonyl)benzene boronic acid in presence of aqueous sodium carbonate and *tetrakis*-triphenylphospine palladium (0) produced in 80 % yield. Reduction of this intermediate with sodium borohydride furnished [2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methanol (**11**) in 95 % yield. Reaction of intermediate **11** with methane sulphonyl chloride at low temperature afforded the key intermediate 4,4-dimethyl-2-(4'-methanesulfonyloxymethylbiphenyl-2-yl)oxazoline (**12**) in 99 % yield (**Scheme-III**).



Scheme-III. Reagents and conditions: (a) NaH, THF, dimethyl acetamide, 8.0 h, 85 % (b) Concentrated hydrochloric acid, reflux, 30.0 h, 85 %

In summary, an improved and convergent approach to the biphenyl oxazoline structure of telmisartan **1** has been developed by employing Suzuki coupling and an intermediate the key intermediate 4,4-dimethyl-2-(4'-methanesulfonyloxy methylbiphenyl-2-yl)oxazoline.

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