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An Improved Synthesis of Telmisartan: An Antihypertensive Drug

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ABSTRACT

An improved synthesis of the angiotensin II receptor antagonist telmisartan is described. It involves Suzuki coupling of 4-formylphenylboronic acid with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline followed by construction of benzimidazole moiety regioselectively though a reductive amination-condensation sequence, replacing the earlier alkylation of the preformed benzimidazole route. This methodology overcomes many drawbacks of the reported syntheses.

Keywords: Telmisartan, antihypertensive drug, Suzuki coupling, oxazoline hydrolysis.

INTRODUCTION

Telmisartan **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. ®

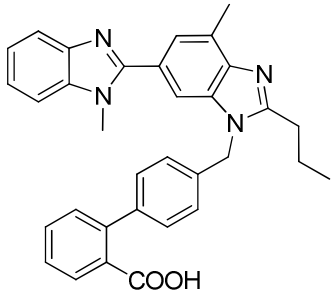

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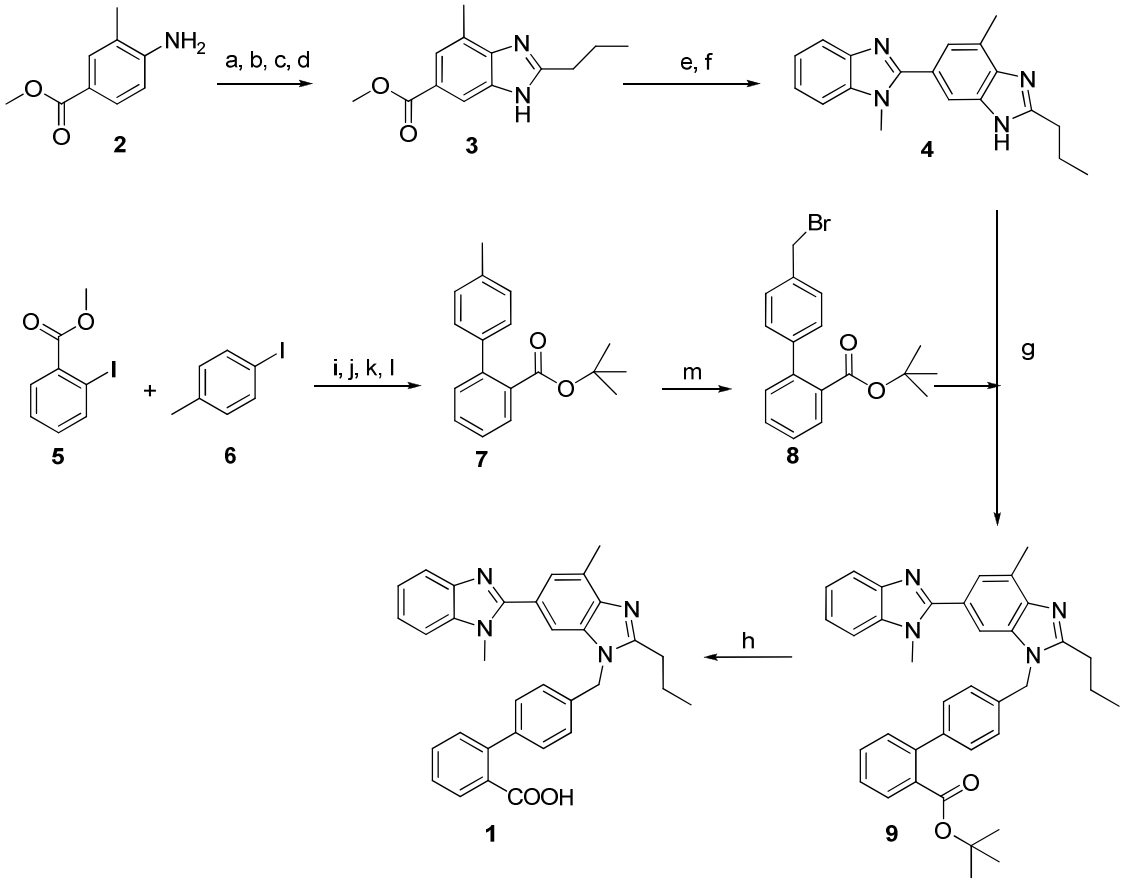
Figure 1. the Angiotensin II receptor antagonist telmisartan

The first total synthesis of telmisartan as introduced by Ries et al. (Scheme 1) starts with the acylation of the 4-amino-3-methylbenzoic acid methyl ester **2** with butyryl chloride, followed by nitration, reduction of the nitro group, and subsequent cyclization of the resulting amine to the benzimidazole derivative **3**. After its saponification, the free carboxyl group is condensed with *N*-methyl-1,2-phenylenediamine to afford the bis-benzimidazole **4**. It is finally alkylated with the 4′-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester **8** to give telmisartan **1** after hydrolysis of the ester group (21% overall yield) involving lengthy eight step sequence (3).

First literature synthesis of telmisartan



Scheme 1: (a) ^{n}PrCOCl, C_6H_5Cl, 100 ^{o}C (b) HNO_3/H_2SO_4, 0 ^{o}C (c) Pd/C, 5 bar, H_2, MeOH (d) AcOH, 120 ^{o}C, yield : 78% (e) NaOH, MeOH/H_2O, 100 ^{o}C (f) 2- MeNH-C_6H_4- NH_2, PPA, 150 ^{o}C, yield 64% (g) ^{t}BuOK, DMSO, RT (h) TFA, DCM, RT, yield: 42% (i) Cu (5 eq), 210 ^{o}C, (j) HCl, H_2O, 100 ^{o}C (k) $(COCl)_2$, DCM, 0 ^{o}C, (l) ^{t}BuOK, THF, RT, yield: 9% (m) NBS, $(PhCOO)_2$, CCl_4, 76 ^{o}C

Several improvements to this reaction sequence have been reported, e.g., the use of KOH instead of potassium *tert*-butoxide in the penultimate step and the use of methanolic HCl solution instead of trifluoroacetic acid in the final step [4]. However, the main shortcomings of the synthesis remained viz., the unsatisfactory regioselectivity in the alkylation of **8** with **4**, the poor stability and shorter shelf life of 4'-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **8**, the non

selective and moderately yielding free radical bromination of expensive intermediate **8** and the intricate synthesis of the biaryl intermediate **7**. In the original protocol, the biaryl intermediate **7** was synthesized via an Ullmann coupling of the aryl iodides **5** and **6** using Five equiv of copper [5]. Modern syntheses of **7** involve cross-couplings of sensitive aryl magnesium[6], zinc [7] or boron [8, 9] compounds with alkyl 2-halobenzoates.

In designing an alternative synthesis of telmisartan our goal was to minimize the use of expensive and hazardous metals, circumvent the bromination step, and increase the overall efficiency of the synthesis. This was accomplished by reversing the order of the major bond disconnections. We realized biaryl synthesis and reductive amination are the key steps, and have the potential to overcome both of these weaknesses.

MATERIALS AND METHODS

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 plates. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz & 100 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 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-carbaldehyde (12): To a mixture of 4-formyl phenylboronic acid (**10**, 5.0 g, 0.032 mol) and 2-(2-bromophenyl)-4, 4-dimethyl-2-oxazoline (**11**, 10.1 g, 0.039 mol) in tetrahydrafuran (50 mL), 2M aqueous sodium carbonate solution (20 mL) was added at room temperature. The resulting biphasic solution was degassed with nitrogen gas for 20 minutes. Then Tetrakis(triphenyl- phosphine)palladium (0) (0.25 g) was added to the reaction mixture and heated to reflux (64 ^{o}C). By maintained concentrated temperature for 12 h. After completion of the reaction, the reaction mixture was cooled to 26 ^{o}C and to this was added saturated ammonium chloride solution (50 mL) and ethyl acetate (50 mL). Separated organic layer was washed twice with water (2 x 50 mL). The dried over sodium sulfate and evaporated under vacuum. The residue was chromatographed on silica gel and elution with hexane /ethyl acetate (80:20) the title compound (12) as an oil (7.5 g, 80%); MS (m/z): 280 [M^{+} + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 10.0 (1H, s, -CHO), 7.91 (2H, d, J = 8.4 Hz, ArH), 7.73 (1H, d, J = 8.4 Hz, ArH), 7.48 (2H, d, J = 7.8 Hz, ArH), 7.44-7.34 (2H, m, ArH), 7.30 (1H, m, J = 7.4 Hz, ArH), 3.80 (2H, s, -CH_2), 1.12 (6H, s, 2 x -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 26.9, 66.6, 78.5, 126.7, 127.0, 128.1, 128.4, 128.8, 128.9, 129.3, 129.6, 134.1, 139.3, 146.5, 162.2, 191.0.

1-((2'-(4,4-dimethyl-4,5-dihydro oxazol-2-yl) biphenyl-4-yl)methyl)-4-methyl-2-propyl -1H-benzo[d]-imidazole-6-carboxylic acid (16): A mixture of amine (**13,** 6.0 g, 0.024 mol), aldehyde (**12,** 6.7 g, 0.024 mol), and *p*-TsOH (0.5 g) were suspended in toluene (60 mL) under nitrogen, and the mixture was refluxed for 16 h and then concentrated. The residue was diluted with methanol (60 mL) and then transferred in to a stainless steel autoclave. To the reaction

mixture added activated palladium on charcoal (10%, 1.0 g), and stirred under H_2 pressure (7 bar) for 24 h at 60 °C. It was cooled to room temperature, filtered and the filter cake was rinsed with ethyl acetate (3 x 50 mL). The filtrate was washed with water, and the aqueous layer was basified to pH 10 with aq ammonia and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated. In vacuum to get the crude product (**14**). It was diluted with glacial acetic acid (60 mL), and the resulting solution was refluxed for 2 h and then concentrated. To the obtained residue (**15**), methanol (30 mL), water (30 mL) mixture was added followed by sodium hydroxide (9.6 g, 0.24 mol) and heated to reflux for about 5 h. After completion, the reaction mass was cooled to 25-35 °C and the pH of the reaction was adjusted to 4.5-5.0 using concentrated hydrochloric acid (16). Then the reaction mass continued stirring for 45- 60 min and the crystalline solid obtained was filtered, washed with water (20 mL) and dried at 55-60 °C for 2-3 h (8.0 g, 70%). Mp: 112-116 °C; MS (m/z): 482 [M + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.86 (1H, s, ArH), 7.62- 7.51 (3H, m, ArH), 7.43 - 7.37 (2H, m, ArH), 7.28- 7.26 (2H, d, J = 8.0 Hz, ArH), 7.08- 7.06 (2H, d, J = 8.0 Hz, ArH), 5.60 (2H, s, -CH_2), 3.72 (2H, s, -CH_2), 2.87 (2H, t, J = 7.6 Hz, -CH_2), 2.56 (3H, s, -CH_3), 1.88 (2H, m, J = 7.6 Hz, -CH_2), 1.12 (6H, s, 2 x -CH_3), 0.97 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ ppm): 14.2, 16.9, 21.6, 28.6, 29.6, 31.5, 47.0, 67.6, 79.0, 112.3, 126.1, 126.3, 127.0, 127.2, 127.5, 127.7, 128.8, 129.1, 130.2, 136.9, 137.1, 139.4, 140.6, 143.8, 154.2, 164.1, 171.3.

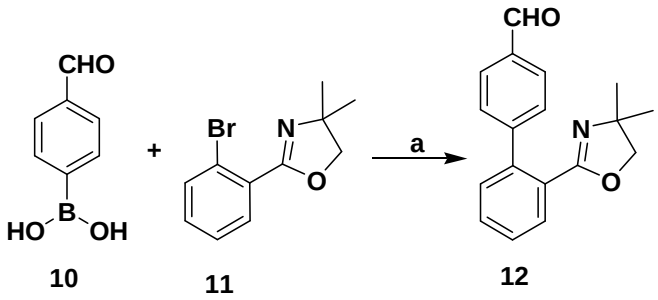
3'-{[2'-(4,4-dimethyl- 4,5-dihydro-1,3-oxazol-2-yl) biphenyl-4-yl]methyl}-1,7'-dimethyl-2'-propyl-1H,-3'H-2,5'-bibenzimidazole (17): A solution of 1-((2'-(4,4-dimethyl-4,5-dihydro oxazol-2-yl) biphenyl-4-yl)methyl)-4-methyl-2-propyl-1H-benzo[d]imidazole-6-carboxylic acid (**16**, 4.0 g, 0.0083 mol) and 1,1′-carbonyldiimidazole (2.0 g, 0.012 mol) in 1,4-dioxane (40 mL) was stirred under nitrogen at room temperature. *N*-Methyl-1,2-phenylenediamine (1.5 g, 0.012 mol) was added to the reaction mixture and refluxed for 4 h. It was cooled room temperature poured into ice cold water (200 mL) and basified with aq ammonia to pH 9. The separted product was extracted twice with ethyl acetate (2 x 25 mL) and evaporated under vacuum at 55 °C. The obtained residue was triturated with n-hexane (50 mL) to get the solid which was filtered, washed with the same solvent and dried at 50-55 °C for 3-4 h to obtain (**17)** as a colourless crystalline powder (4.0 g, 85%). Mp: 191-193 °C (lit [12, 13] Mp: 260-262 °C); MS (m/z): 568 [M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.78 (1H, d, J = 8.0 Hz, ArH), 7.68 (1H, s, ArH), 7.64 (1H, s, ArH), 7.62- 7.60 (2H, d, J = 8.0 Hz, ArH), 7.59 (1H, d, J = 8.0 Hz, ArH), 7.47- 7.17 (6H, m, ArH), 7.09- 7.07 (2H, d, 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, 2 x -CH_3), 1.04 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (100 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.

4'-[(1,7'-Dimethyl-2'-propyl-1H,3'H-2,5'-bibenz imidazol-3'-yl) methyl] biphenyl-2-carboxylic acid (1) A mixture of (**17**, 4.0 g, 0.007 mol), concentrated hydrochloric acid (40 mL) was heated to reflux (100-105 ^{o}C) for about 30 h. The reaction mass was cooled to 0-5 ^{o}C. Then 20% sodium hydroxide solution was added until the reaction mixture attained to pH 9-10 and further stirred at room temperature for 2 h. The precipitated solid was filtered, washed with water (50 mL) and the wet cake was dissolved in a mixture of water (60 mL) and acetonitrile (20.0 mL) 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 was continued for 2 h. The precipitated solid was filtered washed with water (50 mL) and dried at 70-75 °C for 4-5 h under a vacuum to obtain telmisartan as a colourless crystalline powder (3.0 g, 85 %). Mp: 260-262 °C (lit [4] Mp: 260-262 °C); MS (m/z): 515 [M^+ + 1]; ^{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), 7.52-7.28 (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 (100 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.

RESULTS AND DISCUSSION

We identified 4-formylphenylboronic acid (**10**) and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (**11**) as the ideal starting materials for the preparation of the key biaryl intermediate. Thus, Suzuki coupling of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline [10] with 4-formylphenylboronic acid in presence of aqueous sodium carbonate and tetrakis(triphenylphosphine)palladium(0) in THF gave 2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carbaldehyde (**12**) in over 80% yield (Scheme 2).

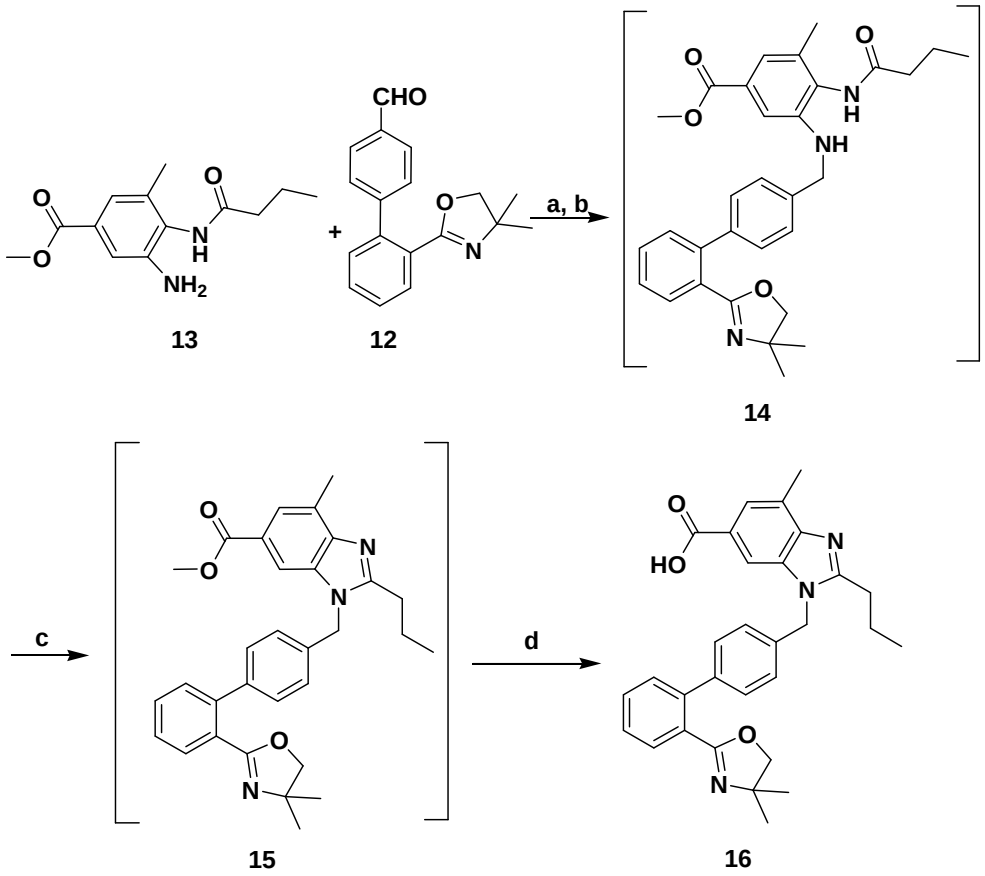


10 **11** **12**

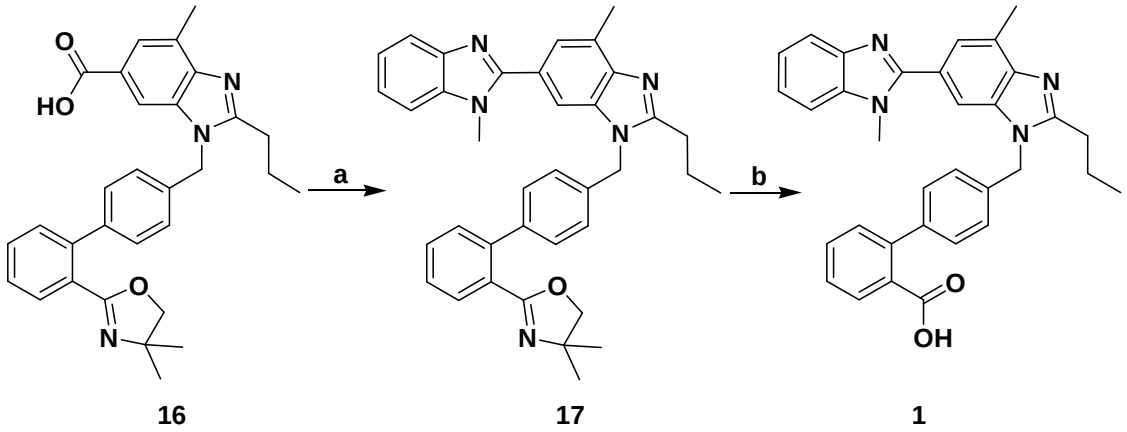
Scheme 2: (a) $Pd(PPh_3)_4$, aq Na_2CO_3, THF, 12 h (80%).

The reaction of biaryl aldehyde **12** with amine **13** (prepared by the literature procedure [4]) was carried out in the presence of *p*-toluenesulfonic acid in toluene to form the corresponding imine, which on hydrogenation in methanol yielded the amine **14.** The amine was not isolated but cyclized in situ to the *n*-propyl benzimidazole **15** in refluxing glacial acetic acid followed by in situ hydrolysis to the acid in 80% yield. (Scheme 3).

The substrate **16**, on attempted dehydrative cyclic condensation with *N*-methyl-1,2-phenylenediamine using polyphosphoric acid at 150 °C led to substantial side reactions such as cleavage of the butyryl group, butyrylation of the diamine and cleavage of oxazoline group and required the intermediate **17** with 30% yield after repeated purifications. An alternative condensation methodology has been adofold by the activation of the carboxylic acid **16** with 1,1'-carbonyldiimidazole (CDI) followed by coupling with *N*-methyl-1,2-phenylenediamine and in situ cyclization in 1,4-dioxane at 130 ^{o}C, afforded the bis benzimidazole derivative **17** in 85% yield. Finally oxazoline intermediate was cleaved by concentrated hydrochloric acid to afford telmisartan **1** (Scheme 4).



Scheme 3: (a) *p*-TsOH, toluene, 110 ^{o}C, 2h (b) Pd/C, 7 bar H_2, MeOH, 60 ^{o}C, 24 h (c) AcOH, 120 ^{o}C, 2 h (d) NaOH, MeOH/H_2O, 70 ^{o}C, 5h (70%).



Scheme 4: (a) CDI, 2- MeNH-C_6H_4- NH_2, 1,4- Dioxane, 130 ^{o}C, 4h (85%) (b) Conc. HCl, 100-110 ^{o}C, 30h (85%).

CONCLUSION

In conclusion, an improved synthesis of the antihypertensive drug telmisartan has been developed, featuring a Suzuki cross-coupling for the construction of the biaryl moiety and a regiospecific reduction of the azomethine followed by cyclic condensation sequence for the synthesis of the central benzimidazole.

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