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Alternative Synthesis of Telmisartan via Suzuki Coupling

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ABSTRACT

*An alternative synthesis of telmisartan one of the most important agents used in antihypertensive therapy is reported. Metalation of 4-bromo toluene provides the key boronic acid ester intermediate **14** for palladium catalysed biaryl coupling with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline **16** via Suzuki coupling. The hydrolysis of oxazoline in telmisartan was realized in a convenient and economical manner, which is more suitable for industrial production. This methodology overcomes many of drawbacks associated with previously 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, 2]. Telmisartan is currently available in the market as an antihypertensive drug [3] under the brand name of MICARDIS.

Essential hypertension is a major risk factor for cardiovascular disease and is responsible for one-third of global deaths. Most antihypertensive drugs interact with the renin-angiotensin system (RAS), which is the central regulator of blood pressure and electrolyte homeostasis. Renin transforms angiotensinogen into the decapeptide angiotensin I, which is converted by the angiotensin conversion enzyme (ACE) into the octapeptide angiotensin II. The latter binds to its angiotensin receptor (AT1) and, thereby, becomes a powerful vasoconstrictor. In the early 1990s, Merck introduced the nonpeptidic orally active angiotensin II receptor antagonist losartan (Lozaar) as the first member of a new class of antihypertensive drugs called sartans, which contain a characteristic *ortho* functionalized biaryl moiety. Telmisartan (**1**, Boehringer Ingelheim, Micardis) (Figure 1) is an important member of this class of top-selling drugs because

it has the strongest binding affinity to the AT1 receptor, an excellent bioavailability, and a once daily dosage.

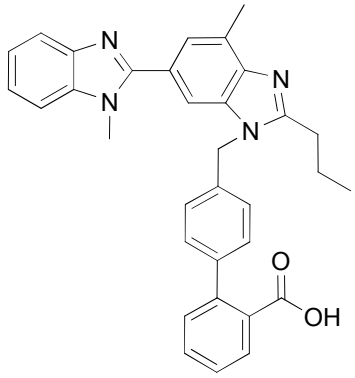

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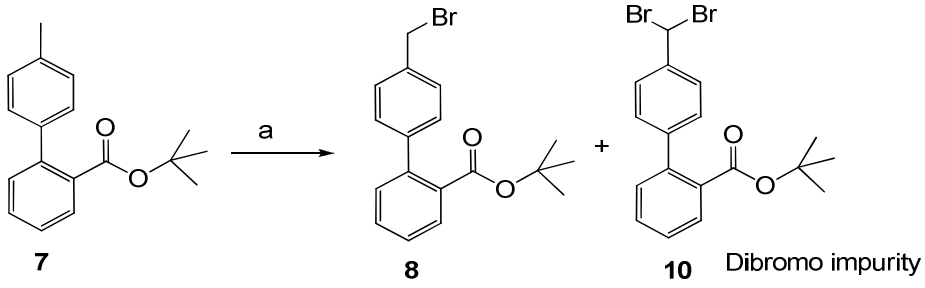
Figure 1. The angiotensin II receptor antagonist telmisartan

The first total synthesis of telmisartan as introduced by Ries et al. (**Scheme 2**) 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**, which is finally alkylated with the 4′-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester **8** to give telmisartan **1** after hydrolysis of the ester group in 21% overall yield and eight steps over the longest sequence[4].

Several improvements to this reaction seqence 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 [5]. However, the main shortcomings of the synthesis remained, namely, the unsatisfactory regioselectivity in the alkylation of **8** with **4** and the intricate synthesis of the biaryl intermediate **7**. In the original protocol, it was synthesized via an Ullmann coupling of the aryl iodides **5** and **6** using 5 equiv of copper. Modern syntheses of **7** involve cross-couplings of sensitive aryl magnesium, zinc, or boron compounds with alkyl 2-halobenzoates. Since the commercialization of telmisartan, **7** has become easily available at low cost, so that most subsequently published procedures start from this compound.



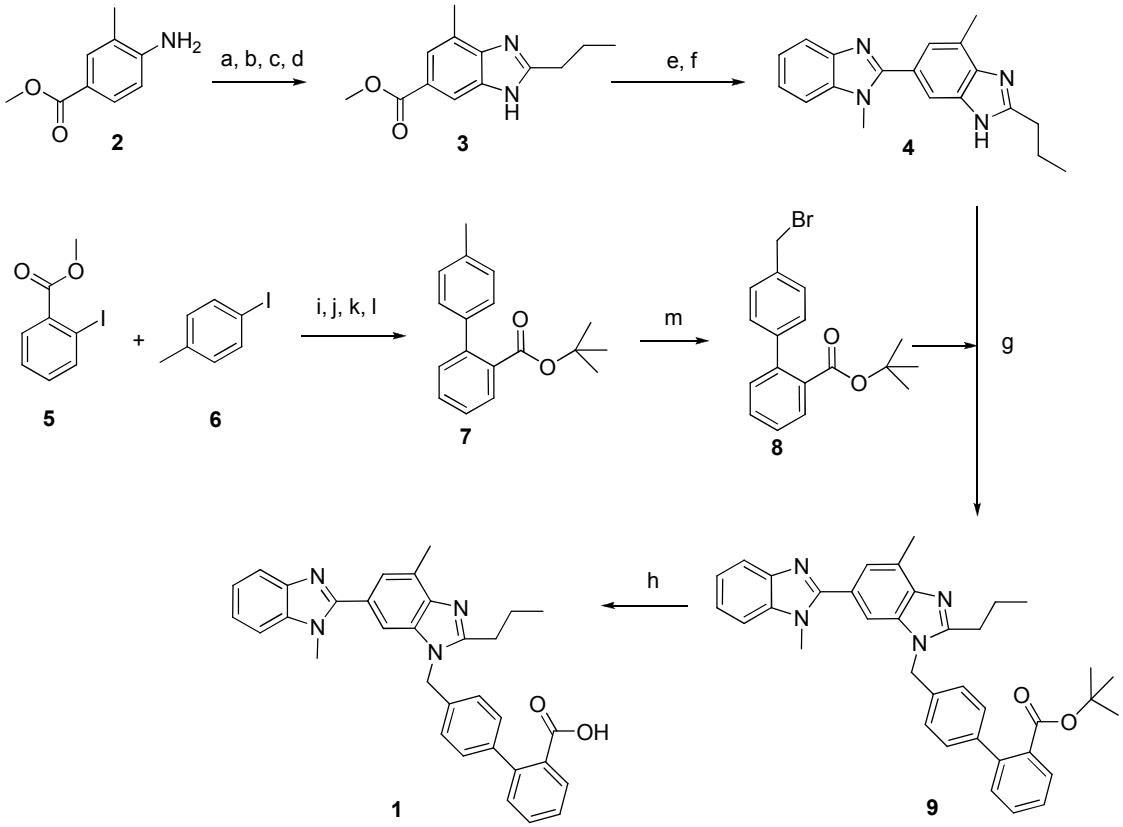
7 **8** **10**

Scheme 1*:* (a) N-bromosuccinamide, AIBN, CCl_4, reflux, 5.0 h, 50- 75%.

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 **8** (c) low yield and purity

obtained during the preparation of 4'-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester **8** due to the formation of 20-45% of dibromo impurity **10** in bromination step (**Scheme 1**).

First literature synthesis of telmisartan



Scheme 2 *:* (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

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.

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 $60F_{254}$ 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.

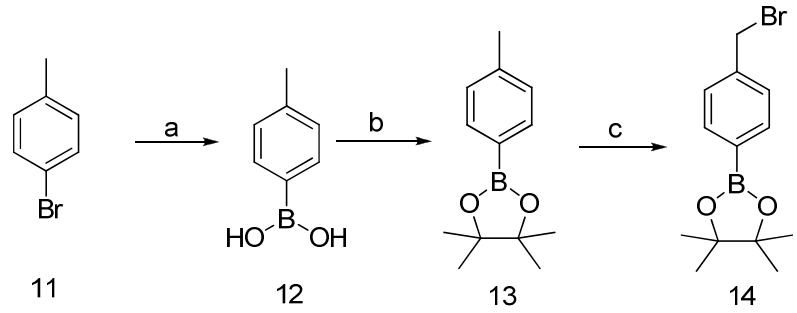
1,7'-dimethyl-2'-propyl-3'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H,3'H-2,5'-bibenzo[d]imidazole (15): A solution of 1,4'-dimethyl-2'-propyl-1H, 3'H-2,5-dibenzimidazole **4**, (3.0 g, 0.009 mol), THF (30 mL) was added dropwise to the mixture of 60% sodium hydride (0.47 g, 0.0108 mol) in THF (30 mL) under inert atmosphere. The reaction mixture was stirred for 30 min at room temperature. 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **14** (3.50 g, 0.011 mol) in THF (30 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 °C, 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 °C. 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 **15** (yield 3.0 g, 60% yield); MS (m/z): 521[M^+ + 1]; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.78 (1H, s, ArH), 7.68 (1H, s, ArH), 7.47-7.26 (6H, m, ArH), 7.07 (2H, m, J = 8.0 Hz, ArH), 5.69 (2H, s, -CH_2), 3.88 (3H, s, -CH_3), 2.87 (2H, t, J = 7.6 Hz, -CH_2), 2.64 (3H, s, -CH_3), 1.89 (2H, m , J = 7.6 Hz, -CH_2), 1.29 (12H, s, 4 x -CH_3), 0.98 (3H, t, J = 7.6 Hz, -CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 14.2, 17.7, 21.6, 23.6, 25.5, 30.2, 31.6, 47.2, 84.2, 109.2, 113.4, 119.3, 123.5, 123.6, 125.4, 125.8, 127.1, 128.0, 131.7, 134.5, 135.6, 137.8, 138.9, 142.6, 144.5, 154.2, 154.5.

2-(4'-((1,7'-Dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzo[*d*]imidazol-3'-yl)-methyl)bi- phenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (17): To a mixture of 1,7'-dimethyl-2'-propyl-3'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H,3'H-2,5'-bibenzo- [d]imidazole **15** (3.0 g, 0.005 mol) and 2-(2-bromo phenyl)-4,4-dimethyl-2-oxazoline **16** (1.7 g, 0.006 mol) in tetrahydrafuran (50.0 mL), 2M aqueous sodium carbonate solution (20.0 mL) was added at room temperature. The resulting bi phasic solution was degassed with nitrogen gas for 20 minutes. Tetrakis(triphenylphosphine)palladium (0) (0.25 g) was added and heated to reflux (64 ^{o}C). The reaction mixture was maintained under reflux for 12 h. After completion of the reaction, the reaction mixture was cooled to 26 ^{o}C 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 (50.0 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 **17** as a white colored solid (2.8 g, 70%); mp 191-193 °C (lit [7] mp191-193 ^{o}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), 7.07 (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 (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.

4'-[(1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzimidazol-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. 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 mL). The wet cake was dissolved in a mixture of water (60 mL) and acetonitrile (20 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 %); mp: 260-262 °C (lit[7] mp 260-262 °C); IR (KBr, cm^{-1}) 2300-3500 (broad), 1680 (C=O); 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 (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.

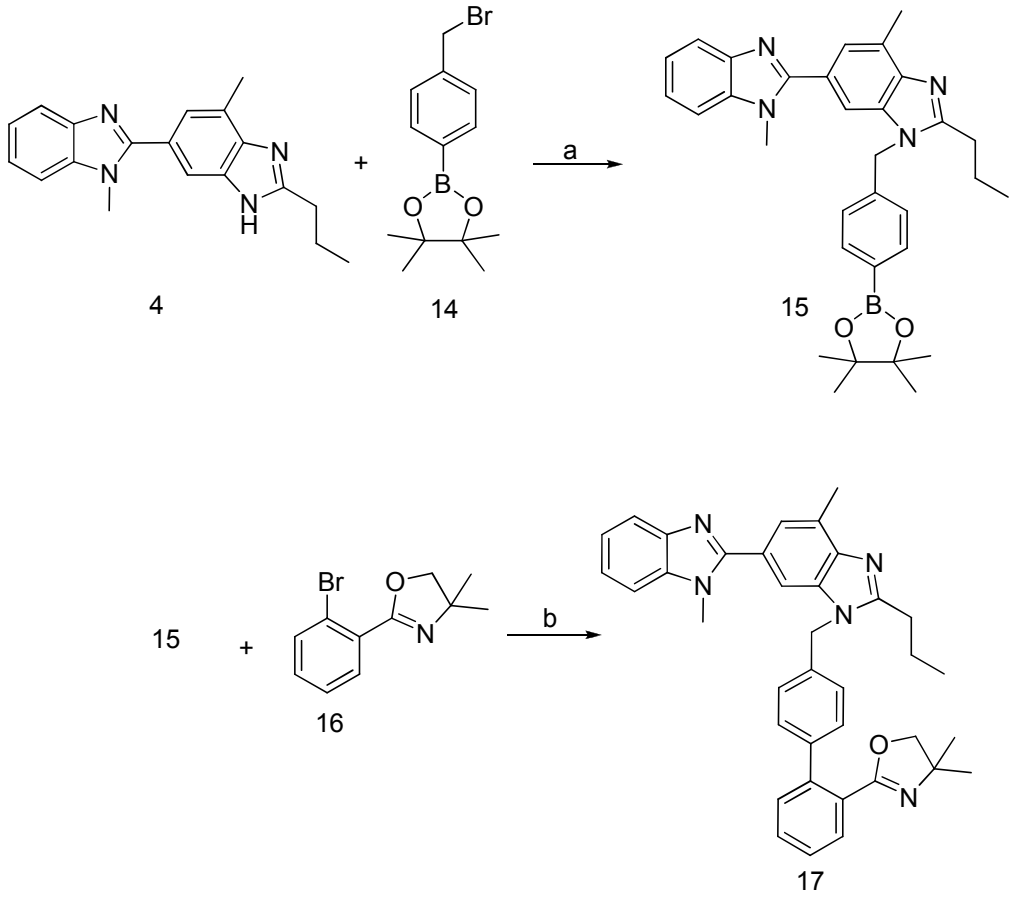
RESULTS AND DISCUSSION

The first segment of our synthesis was construction of 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **14** (**Scheme 3**). First, boronic acid was prepared from 4-bromo toluene **11** by reacting with n-BuLi and triisopropyl borate at -78 ^{o}C and stirred for two hours at the same temperature to afford the *p*-tolyl boronic acid **12** (85%). Second, the mixture of **12** and pinacol in cyclohexane was refluxed for ten hours to remove water and then the 4,4,5,5-tetramethyl-2-p-tolyl-1,3,2-dioxaborolane **13** was obtained in 80% yield. Third, compound **13**, NBS and AIBN in cyclohexane were refluxed for five hours to provide the intermediate **14** (82%).

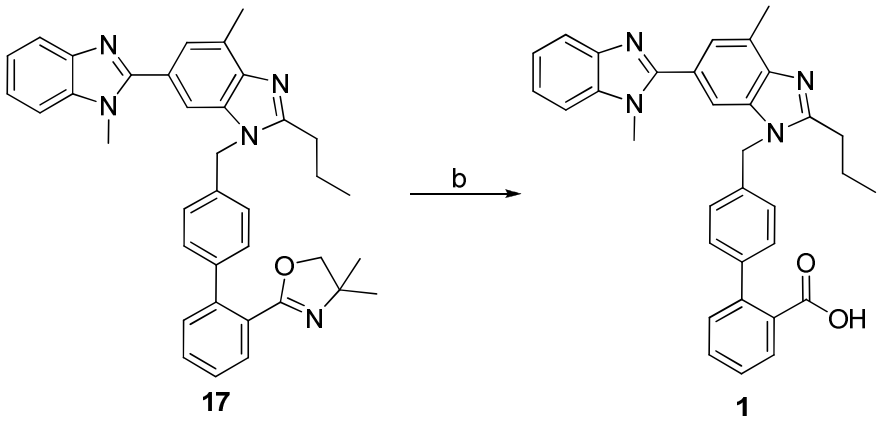


Scheme 3: (a) n-BuLi, triisopropyl borate, THF, -70 ^{o}C (b) pinacol, cyclohexane, 85 ^{o}C (c) NBS, AIBN, Cyclohexane, 85 ^{o}C

The second segment is the preparation of the key intermediate **15** for Suzuki coupling (**Scheme 4**). First , 1,7'-dimethyl-2'-propyl-1*H*,3'*H*-2,5'-bibenzo[*d*]imidazole **4,** sodium hydride and 2-(4-(bromomethyl)- phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **14** in THF were allowed to heated at 70 ^{o}C for three hours to give 1,7'-dimethyl-2'-propyl-3'-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1H,3'H-2,5'-bibenzo[d]imidazole **15** (60%).



Scheme 4: (a) NaH, THF, 25-30 ^{o}C (b) Na_2CO_3, $Pd(PPh_3)_4$, THF, 80 ^{o}C.



Scheme 5: (a) Concentrated HCl, 105- 110 ^{o}C, 30 h

Finally biaryl coupling, which was conducted with the borate ester 15 and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline [6] 16 in presence of sodium carbonate and Pd(PPh3)4 at 80^{o}C for 48 hours to afford the coupling product 17 in 70% (scheme 4). The third segment of our synthesis was deprotection oxazoline to carboxylic acid. Hydrolysis of oxazoline 17 is carried out by

refluxing in concentrated hydrochloric acid for 30 hours at 105-110^{o}C to afford the telmisartan 1in 85% **(Scheme 5).**

CONCLUSION

In summary, greatly efficient and convergent approach to the telmisartan has been developed by employing the Suzuki coupling method. To the best of knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to high yields.

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