An improved synthesis of Telmisartan: an antihypertensive drug

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Abstract

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 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole of Telmisartan, N-alkylation and oxazoline hydrolysis.

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.
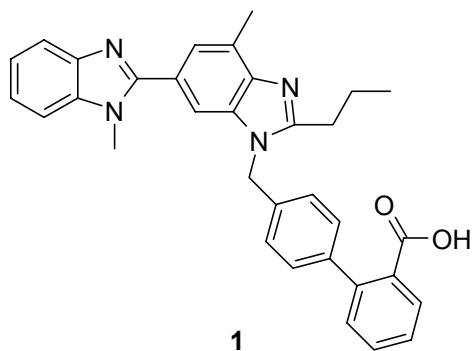
The reported synthesis[3,7,8] of Telmisartan in (Scheme 1) involves condensation of 7-methyl-2-propyl-3*H*-benzimidazole-5-carboxylic acid derivative **2** with diamine derivative *N*-methylbenzene-1,2-diamine **3** to get the dibenzimidazole derivative **4.** Alkylation of compound **4** with 4'-bromomethyl-biphenyl-2-carboxylic 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[4] **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.
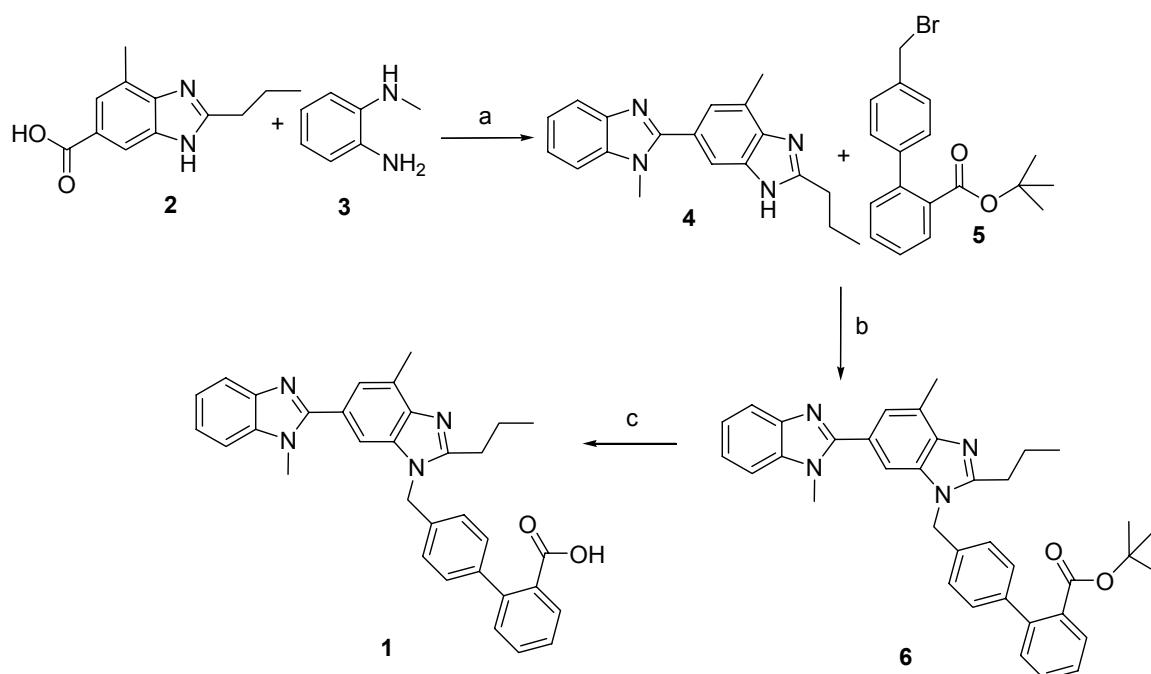
Scheme 1. *Reagents and conditions:* (a) Polyphosphoric acid, 150-155 °C, 4.0 h, 80%. (b) KOt-Bu, Dimethyl acetamide, 75-80 °C, 3.0 h, 70%. (c) Trifluoroacetic acid, DMF, 4.0 h, 70%

The intermediate 4'-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **5,** could not be stored because of its poor stability and shorter shelf life. Therefore, it was used immediately after its preparation. Due to its high reactivity, the ester has the disadvantage of being liable to decomposition and give side reactions, thereby producing a product of low purity.

Also, N-bromosuccinimide used for the preparation of 4'-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **5** has a disadvantage, as this unsuitable for the industrial production because of its cost and reactivity. It is also difficult to control the reaction and avoid the formation of undesired 4'-dibromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **7**

(dibromo impurity) (Scheme 2). 4'-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **5**, is difficult to prepare and has the disadvantages in poor working efficiency and safety, as an intermediate for industrial production.
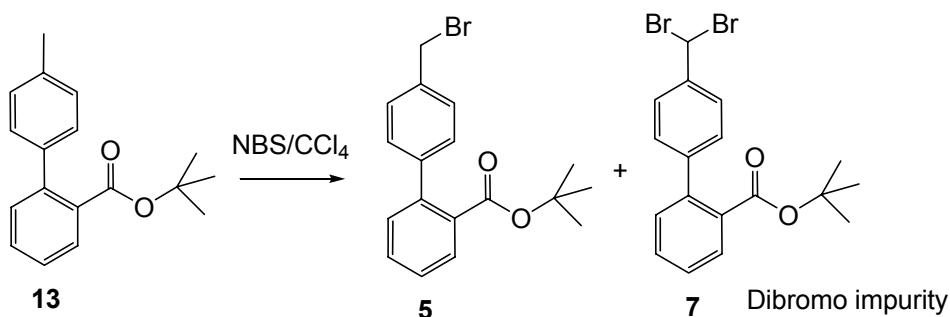

Scheme 2. *Reagents and conditions:* N-bromosuccinamide, AIBN, CCl₄, reflux, 5.0 h, 50-75%.

In the present communication, we report the use of 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole[5] **12**, which has an excellent shelf life (Scheme 3). 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.

Results and Discussion

In our attempts to prepare Telmisartan **1**, we have developed an improved three-stage process employing Suzuki-coupling[9,10] for the preparation of 2-[4'-(chloromethyl) biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole **12**. Subsequent alkylation with dibenzimidazole derivative[7,8] **4** and acid hydrolysis of intermediate **13** provided Telmisartan **1** in good yield.

We have identified 4-formyl phenylboronic acid **8** and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline[6] **9** (prepared as per literature procedure cited as reference number 6) as key starting materials for the preparation of key intermediate 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole **12**. Suzuki coupling was accomplished for the preparation of intermediate, 2'-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carbaldehyde **10** by reacting 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline with 4- formyl phenylboronic acid in presence of aqueous sodium carbonate and tetrakistriphenylphospine 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. Chlorination of intermediate **11** with thionyl chloride at low temperature afforded the key intermediate 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole **12** in 99% yield (Scheme 3).
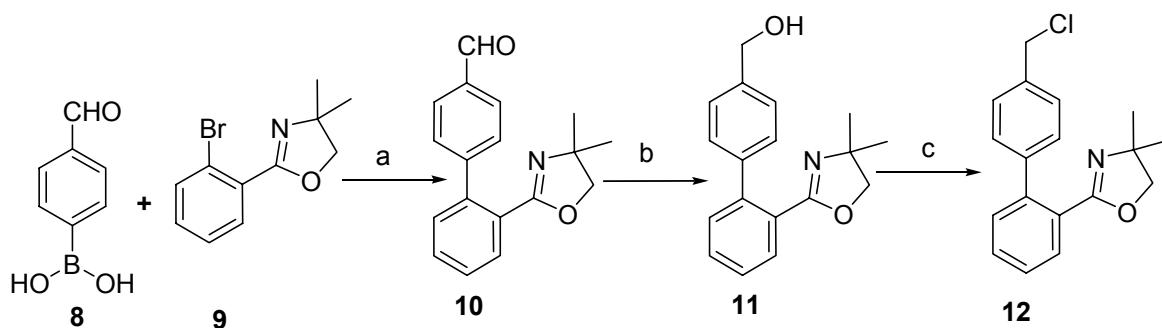
Scheme 3. *Reagents and conditions:* (a) Pd(PPh$_3$)$_4$, aq Na$_2$CO$_3$, THF, 12.0 h, 80%. (b) NaBH$_4$, Ethanol, THF, 3.0 h, 95%. (c) Thionyl chloride, DCM, 2.0 h, 99%.
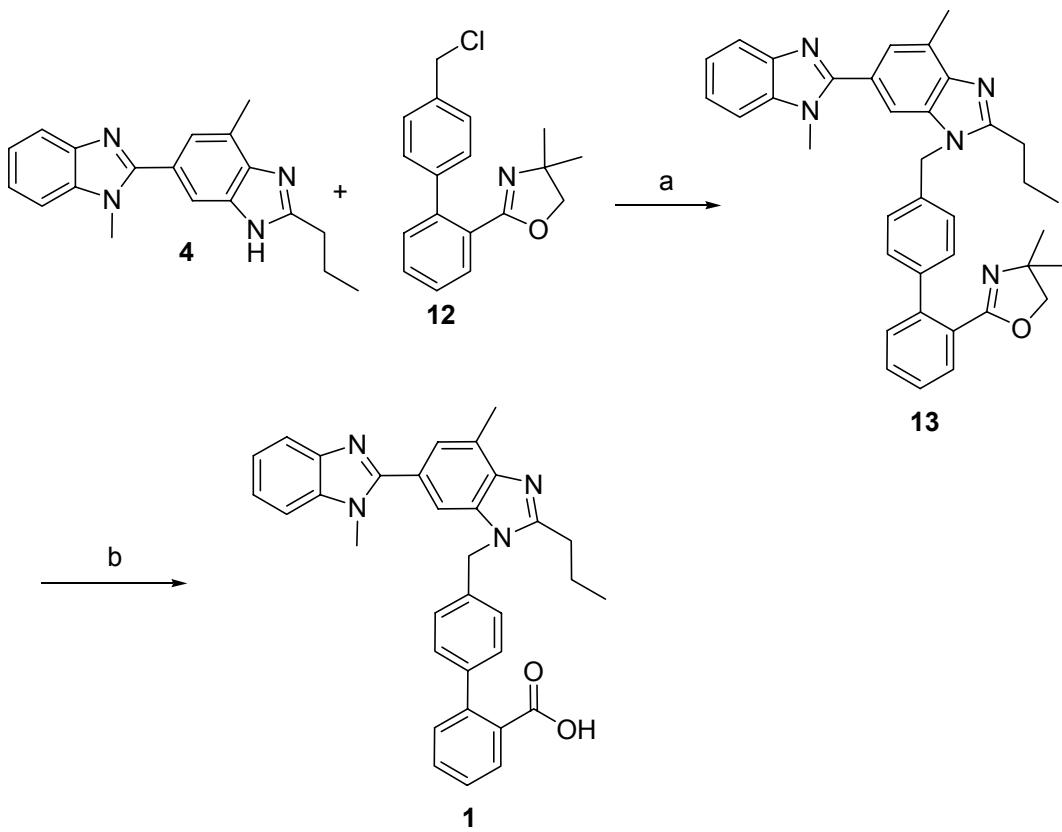
Scheme 4. *Reagents and conditions:* (a) NaH, THF, Dimethyl acetamide, 8.0 h, 85%. (b) Concentrated hydrochloric acid, reflux, 30.0 h, 85%.

In summary, an improved and convergent approach to the biphenyl oxazoline structure of Telmisartan **1** has been developed by employing Suzuki coupling in the synthesis of the key intermediate 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxaz- ole **12**.

Experimental Section

General Procedures. 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-carbaldehyde (10). To a mixture of 4-formyl phenylboronic acid **8** (5.0 g, 0.032 mol) and 2-(2-bromophenyl)-4, 4-dimethyl-2-oxazoline **9** (10.1 g, 0.039 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. Tetrakistriphenyl phosphine 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, the drying agent filtered off and the organic solution 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 (7.5 g, 80%); ^{1}H NMR (400 MHz, DMSO-d$_6$) (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, 2x-CH$_3$); ^{13}C NMR (400 MHz, DMSO-d$_6$) (δ ppm); 28.0, 68.0, 78.9, 128.0, 128.5, 129.5, 129.6, 130.4, 130.5, 131.2, 135.3, 140.2, 147.0, 161.8, 193.2.; MS (m/z): 280 [M$^+$ + 1].; Anal. Calcd for C$_{18}$H$_{17}$NO$_2$ (279): C, 77.40; H, 6.13; N, 5.01; O, 11.46. Found: C, 77.21; H, 6.10; N, 5.04.

[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-carbaldehyde **10** (1.0 g, 0.035 mol) in THF and ethanol 1:1 mixture (20.0 mL), sodium borohydride (0.4 g, 0.0105 mol) was added portionwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was cooled to 5-10 °C and poured into a solution of saturated aqueous ammonium chloride (30 mL). To this was added of ethyl acetate (25.0 mL), separated organic layer and washed twice with water 20.0 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 give the title compound **11** as a white solid (0.91g, 95%); melting point: 98-100 °C (lit^5 mp 97-100 ^{o}C); ^{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; O, 11.37. Found: C, 77.02; H, 6.81; N, 4.90.

2-[4'-(Chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (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 thionyl chloride (2.0 g, 0.017 mol) drop wisely at 0-5 ^{o}C and maintained for 2 h. The reaction mixture was poured into an aqueous solution of 20% of sodium hydrogen carbonate solution (40.0 mL). Separated the organic layer was washed twice with water (50.0 mL). The organic layer was concentrated under pressure to give the title compound **12** as a white solid (4.2 g, 99% yield); melting point: 73-75 °C (lit^5 mp 73-75 ^{o}C); ^{1}H NMR (400 MHz, CDCl$_3$) (δ ppm): 7.75 (1H, m, J = 7.4 Hz, ArH), 7.62 (1H, m, J = 7.4 Hz, ArH), 7.43-7.35 (6H, m, ArH), 4.64 (2H, s, -CH$_2$), 3.81 (2H, s, -CH$_2$), 1.29 (6H, s, 2x-CH$_3$); ^{13}C NMR (400 MHz, CDCl$_3$) (δ ppm); 32.1, 50.2, 71.7, 83.6, 131.4, 132.0, 132.4, 132.9, 134.2, 134.3, 134.6, 140.5, 145.1, 145.4, 167.7.; MS (m/z): 300 [M$^+$ + 1]; Anal. Calcd for C$_{18}$H$_{18}$ClNO: C, 72.11; H, 6.05; Cl, 11.83; N, 4.67; O, 5.34. Found: C, 72.21; H, 6.10; N, 4.68.

3'-{[2'-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-yl]methyl}-1,7'-dimeth-yl-2'-propyl-1*H*,3'*H*-2,5'-bibenzimidazole (13). A solution of 1,4'-dimethyl-2'-propyl-1H, 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 30 min at room temperature. 2-[4'-(chloromethyl)biphenyl-2-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole **12** (3.5 g, 0.011 mol) in THF (30 mL) and dimethylacetamide (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 °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 **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$_5$O: C, 78.28; H, 6.57; N, 12.34; O, 2.82. 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 ^{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. The precipitated solid was collected by filtration 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] mp 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$_4$O$_2$: C, 77.02; H, 5.88; N, 10.89; O, 6.22. Found: C, 77.0; H, 5.82; N, 10.86.

Acknowledgements

References

1. (a) Battershill, A. J.; Scott, L. *J. Drugs* **2006**, *66*, 51 (b) Norbert, H.; Berthold, N.; Uwe, R.; Jacobus, C. A.; Van, M.; Wolfgang, W.; Michael, E. U.S. Patent 5,591,762, 1997. (c) Ruth, R. W.; William, J. C.; John, D. I.; Michael, R. C.; Kristine, P.; Ronald, D. S.; Pieter, B. M. W. M. T. *J. Med. Chem.* **1996**, *39*, 625.
2. http://www.rxlist.com/cgi/generic2/telmisartan.htm.
3. (a) Uwe, J. R.; Gerhard, B. N.; Kai, M. H.; Helmut, W.; Michael, E.; Jacobus, C. A.; Van, M.; Wolfgang, W.; Norbert, H. H. *J. Med. Chem.* **1993**, *36*, 4040. (b) Merlos, M.; Casas, A.; Castaner, *J. Drugs Future* **1997**, *22*, 1112.
4. Carini, D. J.; Dunicia, J. V. Eu. Patent 2,53,310, 1988
5. Yosiro Urawa; Ken furukawa; Toshikazu; yoji yamagishi, all of Ibaraki; Tomio Tsurugi, Chiba; Tomio Ichino. U.S. Patent 5,557,002, 1996.
6. Marxer, Rodriguez, McKenna, and Tsai. *J. Org. Chem.* **1975**, *40*, 1427.
7. Venkataraman, S.; Mathad, V. T.; Kikkuru, S. R.; Neti, S.; Chinta, R. R.; Arunagiri, M.; Routhu, L. KPCT WO 06/044754A2, **2006**.

8. Venkataraman, S.; Mathad, V. T.; Kikkuru, S. R.; Neti, S.; Chinta, R. R.; Apuraba, B.; Anjaneyulu,Y.; Naveenkumar, K. *Org. Process Res. Dev.* **2007**, *11*, 81.

9. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. The Stille reaction has also been widely applied in biaryl synthesis: (c) Stanfort, S. P. *Tetrahedron* **1998**, *54*, 263. (d) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (e) Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001. (f) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054. (g) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

10. For recent examples, see: (a) Dupuis, C.; Adiey, K. Charruault, L.; Michelet, V.; Savignac, M.; Genet, J.-P.*Tetrahedron Lett.* **2001**, *42*, 6523. (b) Feuerstein, M.;Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667. (c) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757. (d) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (e) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540. (f) Vaz, B.; Rosana, R.; Nieto, M.; Paniello, A. I.; deLera, A. R. *Tetrahedron Lett.* **2001**, *42*, 7409. (g) Wang, W.; Xiong, C.; Yang, J.; Hruby, V. J. *Tetrahedron Lett.***2001**, *42*, 7717. (h) Zhuravel, M. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 7925. (i) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125. (j) Netherton, M.R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (k) Yin, J.; Rainka,M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (l) Molander, G. A.; Rivero, M. R. *Org. Lett.***2002**, *4*, 107.