Efficient and improved synthesis of Telmisartan
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Abstract
An efficient synthesis of the angiotensin II receptor antagonist Telmisartan (1) is presented involving a cross coupling of 4-formyl-phenylboronic acid 10 with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (11) as the key step (90% yield). The benzimidazole moiety 15 was constructed regioselectively via a reductive amination-condensation sequence, replacing the alkylation of the preformed benzimidazole step in the previously published route. This methodology overcomes many of the drawbacks associated with previously reported syntheses.

Introduction
Telmisartan (1) is an angiotensin II receptor antagonist useful in the treatment of hypertension, heart diseases, heart attack, and bladder diseases [1-3]. Telmisartan is currently available in the market as an antihypertensive drug [4] under the brand name of Micardis®.

Essential hypertension is a major risk factor in cardiovascular diseases 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 decapetide 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 non-peptidic orally active angiotensin II receptor antagonist losartan (Lozaar) as the first member of a new class of antihypertensive drugs called sartans, all of 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-per-day dosage.

The first total synthesis of Telmisartan as introduced by Ries et al. (Scheme 1) starts with the acylation of 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 saponification, the free carboxyl group is condensed with N-methyl-1,2-phenylenediamine to afford the bis-benzimida-
Scheme 1: First literature synthesis of Telmisartan (a) PhCOCl, C₂H₅Cl, 100 °C (b) HNO₃/H₂SO₄, 0 °C (c) Pd/C, 5 bar, H₂, MeOH (d) AcOH, 120 °C, yield: 78% (e) NaOH, MeOH/H₂O, 100 °C (f) 2-MeNH-C₆H₄-NH₂, PPA, 150 °C, yield: 64% (g) BuOK, DMSO, RT (h) TFA, DCM, RT, yield: 42% (i) Cu (5 equiv), 210 °C, (j) HCl, H₂O, 100 °C (k) (COCl)₂, DCM, 0 °C, (l) BuOK, THF, RT, yield: 9% (m) NBS, (PhCOO)₂, CCl₄, 76 °C.
Results and Discussion

We identified 4-formylphenylboronic acid (10) and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (11) \[12\] 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 with 4-formylphenylboronic acid in presence of aqueous sodium carbonate and tetrakis(triphenylphosphine)palladium(0) in THF solvent gave 2’-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)biphenyl-4-carbaldehyde (12) in over 90% yield (Scheme 2).

Scheme 2: (a) Pd(PPh\textsubscript{3})\textsubscript{4}, aq Na\textsubscript{2}CO\textsubscript{3}, THF, 12.0 h, 90%.

The reductive amination of the biaryl aldehyde 12 with amine 13 (prepared by the literature procedure \[13\]) was carried out in the presence of p-toluenesulfonic acid in toluene and followed by hydrogenation in methyl alcohol. The resulting amine 14 was not isolated but cyclized in situ to the n-propyl benzimidazole 15 in 80% yield in refluxing glacial acetic acid. Finally, cleavage of the oxazoline moiety in 15 by acid afforded Telmisartan (1) (Scheme 3).

Conclusion

In conclusion, a concise and selective synthesis of the antihypertensive drug Telmisartan has been developed, featuring a Suzuki cross-coupling for the construction of the biaryl moiety and a regiospecific reductive amination-condensation sequence for the synthesis of the central benzimidazole.

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\textsubscript{254} plates. \textsuperscript{1}H and
13C NMR spectra were recorded in DMSO-d6 and CDCl3 using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS (tetramethylsilane). 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 (12): To a mixture of 4-formylphenylboronic 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 tetrahydrofuran (50.0 mL), 2 M aqueous sodium carbonate solution (50 mL) was added. The mixture was stirred under H2 pressure (7 bar) for 24 h at 60 °C. After cooling to room temperature and filtration, the filter cake was washed with water (3 × 50 mL) and then concentrated. Water (150 mL) was added to residue. The product was extracted twice with ethyl acetate (2 × 50 mL) and evaporated under vacuum at 55 °C. The residue was triturated with n-hexane (40 mL) to yield a solid which was removed by filtration and dried at 50–55 °C for 3–4 h to afford 15 as a white crystalline powder (yield 5.7 g, 80% yield); melting point 191–193 °C; IR (KBr, cm−1) 1630 (C=O); HRMS m/z calculated for C27H37N2O – 568.7225 [M + 1], found – 568.7222; 1H NMR (400 MHz, CDCl3) (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, -CH2), 3.82 (3H, s, -CH3), 2.97 (2H, t, J = 7.6 Hz, -CH2), 2.74 (3H, s, -CH3), 1.92 (2H, m, J = 7.6 Hz, -CH2), 1.29 (6H, s, 2 x -CH3), 1.04 (3H, t, J = 7.6 Hz, -CH3); 13C NMR (100 MHz, CDCl3) (δ ppm): 13.5, 16.7, 20.6, 27.6, 33.0, 39.3, 40.0, 57.0, 70.8, 74.0, 78.9, 79.0, 108.8, 109.2, 119.3, 121.2, 122.2, 123.5, 123.6, 125.6, 127.0, 127.2, 128.8, 129.1, 129.7, 130.2, 130.9, 132.4, 134, 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'-benzimidazol-3'-yl)methyl)biphenyl-2-carboxylic acid (1): A mixture of 15 (4.0 g, 0.007 mol) and concentrated hydrochloric acid (40 mL) was heated at reflux (100–110 °C) for about 30 h. The reaction mass was cooled to 0–5 °C. Sodium hydroxide solution (20%) was added until the pH of the reaction mixture was 9–10 and then stirred at room temperature for a further 2 h. The resulting solid was removed by filtration 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 with 5% acetic acid, and stirring continued for 2 h. The precipitated solid was filtered and washed with water (50 mL). After drying at 70–75 °C for 4–5 h under a vacuum Telmisartan (1) was obtained as a white crystalline powder (yield 2.9 g, 80%); melting point: 260–262 °C (lit [6] mp 260–262 °C); IR (KBr, cm−1) 3300–3500 (broad), 1680 (C=O); HRMS m/z calculated for C37H37N2O – 568.7225 [M + 1], found – 568.7222; 1H NMR (400 MHz, CDCl3) (δ ppm): 12.8 (1H, s, -COOH), 8.42 (1H, d, J = 8.0 Hz, ArH), 8.02 (1H, m, J = 8.0 Hz, ArH), 7.50–7.26 (8H, m, ArH), 7.20 (2H, m, J = 8.0 Hz, ArH), 7.05 (1H, s, ArH), 6.96 (1H, s, ArH), 5.42 (2H, s, -CH2), 3.82 (3H, s, -CH3), 2.97 (2H, t, J = 7.6 Hz, -CH2), 2.74 (3H, s, -CH3), 1.92 (2H, m, J = 7.6 Hz, -CH2), 1.04 (3H, t, J = 7.6 Hz, -CH3); 13C NMR (100 MHz, DMSO-d6) (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.

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