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Improved Synthesis of Valsartan via Nucleophilic Aromatic Substitution on Aryloxazoline

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Improved Synthesis of Valsartan via Nucleophilic Aromatic Substitution on Aryloxazoline

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Abstract: A highly efficient approach to the synthesis of the angiotensin II receptor antagonist valsartan (Diovan), one of the most important agents used in antihypertensive therapy today is described. The formation of the aryl–aryl bond represents the key step of its synthesis, which has been done by simple nucleophelic aromatic substitution on aryloxazoline with good yield and purity.

Keywords: Antihypertensive therapy, nucleophilic aromatic substitution, oxazoline, valsartan

INTRODUCTION

Angiotensin II (A-II) is the principle pressor agent of the renin angiotensin system (RAS), which plays a critical role in the regulation of blood pressure.[1] Prevention of the formation of A-II, via inhibition of angiotensin converting enzyme (ACE),[2] has confirmed the therapeutic benefit of inhibiting the RAS in hypertension and congestive heart failure. This has led to the design and discovery of the nonpeptide A-II receptor antagonist valsartan **1**.[3]

Hypertension is one of the most prevalent diseases in developed countries, with an estimated 1 billion cases worldwide, conferring to its treatment enormous social and economic importance. The therapeutic

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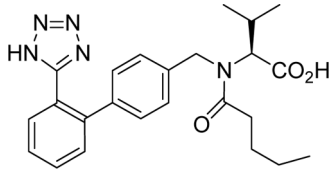

Figure 1. Valsartan (**1**).

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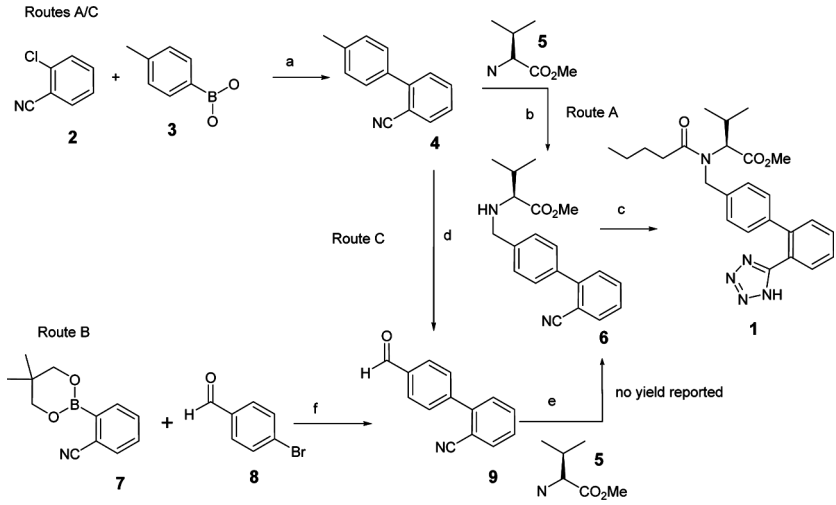
standard was significantly improved in the 1980s by the introduction of losartan (Lorzaar, Merck)[4] as the first nonpeptidic A-II receptor antagonist. An entire therapeutic class, the sartans, has since been developed, among which valsartan (**1**; Diovan, Novartis: US $4.2 billion sales in 2006) (Fig. 1) currently holds the largest market share.

In designing an alternative synthesis for valsartan **1**, our goal was to develop a robust and economic route for valsartan **1** and 2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde **14** by minimizing the use of expensive chemicals and increasing the overall efficiency of the synthesis. We now disclose this highly efficient and industrially viable process for the synthesis of valsartan **1**, with good overall yield.

The structural element, a biphenyl unit, is essential for the binding affinity to the receptor and for oral bioavailability. The formation of its aryl–aryl bond represents the key step in the synthesis of sartans: whereas for the synthesis of losartan, the use of Negishi[5] and Ullmann[6] couplings is described in the literature, but the published methods for the preparation of valsartan make use of Suzuki–Miyaura couplings.[7] The principal synthetic pathways leading to valsartan are depicted in Scheme 1. In route A, 2-chlorobenzonitrile (**2**) and 4-tolylboronic acid (**3**) are coupled to give 2-cyano-4′-methylbiphenyl (**4**), which is then brominated and reacted with L-valine methyl ester (**5**) to give *N*-[(2′-cyanobiphenyl-4-yl)methyl]-L-valine methyl ester (**6**). Alternatively, **6** can be obtained via the coupling of 4-bromobenzaldehyde (**8**) with a boronic acid derivative (e.g., **7**), followed by reductive amination with L-valine methyl ester (**5**) (route B). Route C results from a combination of both approaches, in which the sensitive formyl group in biaryl **9** is generated by oxidation of the more robust derivative **4**.

DISCUSSION

The main shortcoming common to these syntheses originates from the use of expensive boronic acid substrates and palladium catalyst in the



Scheme 1. Reported synthetic scheme for valsartan. Reagents and conditions: (a) Pd-cat., K_2CO_3, H_2O, TBAB, Δ, 2 d, 69%; (b) NBS, 70–90%; (c) $^{n}BuCOCl$, Et_3N, NaN_3, nBu_3SnCl, NaOH, 60–85%; (d) NBS, NaOAc/AcOH, NaOH, Swern oxidation; (e) $NaBH_3CN$, no yield reported; (f) Pd-cat., K_2CO_3, 100°C, 73%.

cross-coupling step. We believed that we could overcome this weakness with the biaryl synthesis recently developed in our group. This method overcomes many of the drawbacks, such as use of expensive boronic acid reagent and Pd catalyst as well, which results in the palladium content in the final active pharmaceutical ingredient (API) associated with the previously reported synthesis.

In our approach, shown in Scheme 2, inexpensive and commercially available O-anisic acid (**10**) was treated with thionyl chloride for the formation of acid chloride, which was treated with 2-amino-2-methyl propane-1-ol (**11**) to get the amide. This was further treated with thionyl chloride to get oxazoline compound (**12**).[8] This oxazoline compound (**12**) was treated with [4-(dimethoxymethyl) phenyl] magnesium bromide, which was prepared from 1-bromo-4-(dimethoxymethyl) benzene (**13**) using magnesium as a metal and a catalytic amount of I_2 for the initiation of the reaction. The nucleophelic aromatic substitution on aryloxazoline is the key step of the synthesis. The coupled compound was taken in tetrahydrofuran (THF), and 1 N was added HCl and stirred at rt for 4 h to get 2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (**14**). This 2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (**14**) was taken in methanol, and L-valine methyl ester hydrochloride was added followed by sodium cyano borohydride at reflux condition for

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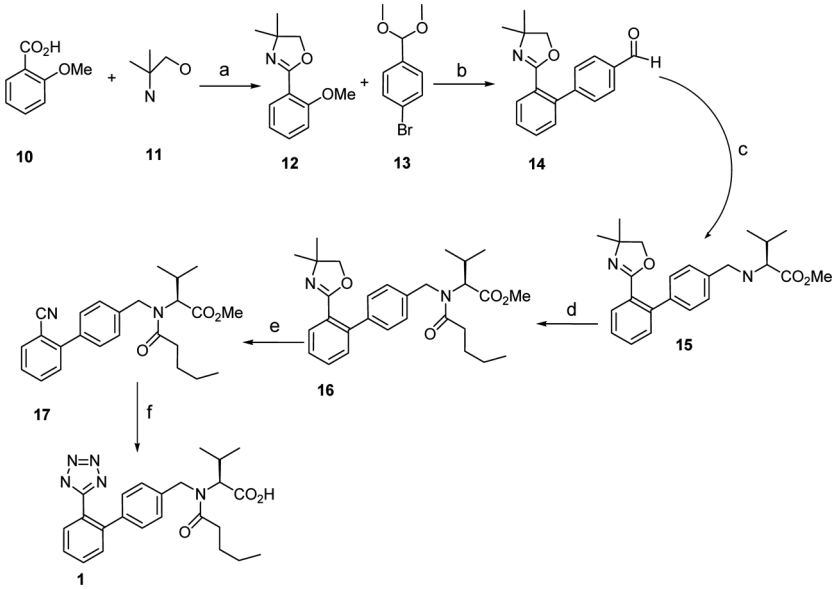

Scheme 2. Modified synthetic scheme for valsartan. Reagents and conditions: (a) $SOCl_2$, DCM, rt, 95%; (b) Mg, THF, I_2, 70°C, 1(N) HCl, 85%; (c) L-valine methyl ester hydrochloride, $NaBH_3CN$, Et_3N, MeOH, 70°C, 90%; (d) pyridine, DCM, 0°C, 90%; (e) $POCl_3$, pyridine, 85°C, 14 h, 90%; (f) NaN_3, Bu_3SnCl, NaOH.

2 h to get 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-amino}-3-methyl-butyric acid methyl ester (**15**). The 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-amino}-3-methyl-butyric acid methyl ester (**15**) was taken in dichloromethane, and valeryl chloride followed by pyridine was added to get 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-pentanoyl-amino}-3-methyl-butyric acid methyl ester (**16**). The 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-pentanoyl-amino}-3-methyl-butyric acid methyl ester (**16**) was taken in pyridine, and phosphorous oxychloride was added at 0°C and heated at 85°C to get 2-[(2′-cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid methyl ester (**17**). Valsartan can be synthesized by sodium azide and tributyl tin chloride.[9]

In summary, a highly efficient approach to the biphenyltetrazole structure of the A-II antagonists has been developed by employing a nucleophelic aromatic substitution on aryloxazoline, which is commercially viable and suitable to plant scale. Application of this approach provided an industrial viable procedure for the synthesis of valsartan, which is a potent, orally active, nonpeptide antagonist of the angiotensin II AT1-receptor subtype.

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EXPERIMENTAL

Materials and Instruments

All solvents and reagents were purchased from the suppliers and used without further purification. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin-layer chromatography (TLC) was performed on Merck precoated silica-gel $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) and $CDCl_3$ on a Varian Gemini 400-MHz Fourier transform (FT) NMR spectrometer. The chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS). The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS instruments.

2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (14)

An oven-dried flask equipped with an internal thermometer, a dropping funnel filled with molecular sieves, and a condenser was charged with magnesium metal (0.7 g, 29.25 mmol), iodine (1 pinch), and 0.5 ml of 1-bromo-4-(dimethoxymethyl) benzene (**13**) in dry tetrahydrofuran (THF; 10 ml). The reaction mixture was heated at 70°C for 30 min. Iodine color was dispersed, and initiation was observed. Then the rest of the 1-bromo-4-(dimethoxymethyl) benzene (5 g, 24.39 mmol) in THF (50 ml) was added slowly dropwise and vigorously refluxed the reaction mass. The refluxation was continued for another 2 h. The reaction mixture was cooled down to rt and transferred via cannula to the oxazoline compound (2 g, 9.7 mmol) (**12**) in THF (40 ml) at 56°C. The reaction mixture was stirred at the same temperature for 16 h. The reaction mixture was monitored by thin-layer chromatography (TLC), and no starting material was left. The reaction mass was cooled down to 0–5°C, and 1.5 N dilute aq. HCl (20 ml) was added to quench the reaction mixture, which was stirred for 1 h. The reaction mixture was washed with methyl *tert*-butyl ether (MTBE) (2 × 50 ml) to remove small impurities. The aq. layer was basified to pH ~7 with 10% aq. $NaHCO_3$ solution, extracted with ethyl acetate (2 × 50 ml), and washed with water. Removal of the solvent afforded the 2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (**14**)[10] as an oil (2.3 g, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H) 7.42–7.91 (m, 8H), 3.76 (s, 2H), 1.12 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 28.09, 68.06, 78.95, 128.05, 128.51, 129.53, 129.69, 130.41, 130.57, 131.22, 135.38, 140.29, 147.00, 161.88,

193.28. ESIMS: m/z calcd. [M+]: 279; found: 280 [M + H+]. HRMS (ESI): m/z calcd. [M+]: 279; found: 280.07 [M + H+].

2-{[2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-amino}-3-methyl-butyric Acid Methyl Ester (15)

L-Valine methyl ester hydrochloride (0.65 g, 3.93 mmol), followed by Et_3N (0.65 ml, 5.37 mmol) and sodium cyanoborohydride (0.292 g, 4.6 mmol), was added to a solution of compound 2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (**14**) (1 g, 3.58 mmol) in methanol (15 ml). The reaction mixture was heated at 70°C for 2 h under an N_2 atmosphere. The reaction was monitored by TLC, and no SM was left. The reaction mixture was cooled down to rt, quenched with water, and extracted with ethyl acetate. The organic layer was concentrated under vacuum to get a crude residue. The crude was purified by column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-amino}-3-methyl-butyric acid methyl ester (**15**) as an pale yellow oil (1.3 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23–7.58 (m, 8 H), 3.74–3.79 (m, 2 H), 3.65–3.72 (m, 2 H) 3.61 (s, 3 H), 2.85–2.86 (d, 1 H), 1.79–1.81 (m, 1 H), 1.22 (s, 3 H), 1.14 (s, 3 H), 0.86–0.88 (3 H, d), 0.81–0.84 (3 H, d). ^{13}C NMR (DMSO-d_6) δ 19.21, 19.66, 28.14, 31.39, 51.38, 51.60, 66.24, 67.89, 78.94, 127.45, 128.05, 128.24, 128.37, 130.26, 130.40, 130.95, 139.20, 139.79, 141.24, 162.54, 175.39. ESIMS: m/z calcd. [M+]: 394; found: 395 [M + H+], 417 [M + + Na]. HRMS (ESI): m/z calcd. [M+]: 394; found: 395.04 [M + H+], 417.08 [M+ +Na].

2-{[2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-pentanoyl-amino}-3-methyl-butyric Acid Methyl Ester (16)

An oven-dried flask was filled with compound 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-amino}-3-methyl-butyric acid methyl ester (**15**) (1.0 g, 2.53 mmol) dissolved in dichloromethane (20 mL) and pyridine (0.26 g, 3.29 mmol) and then cooled to 0°C. Afterward valeroyl chloride (0.397 g, 3.29 mmol) in dichloromethane was added slowly drop by drop under stirring, and the reaction mixture was stirred overnight. The reaction was diluted with water, and the dichloromethane layer was separated and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was concentrated under vacuum and purified through column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-pentanoyl-amino}-3-methyl-butyric acid

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methyl ester (**16**) as a colorless oil (1.1 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09–7.59 (m, 8 H), 4.52–4.74 (m, 2 H), 4.18–4.20 (d, 1 H) 3.71–3.77 (q, 2 H), 3.31–3.36 (d, 3 H), 2.25–2.33 (m, 2 H), 1.90–2.20 (m, 2 H), 1.55–1.6 (m, 1 H), 1.40–1.45 (2 H, m), 1.00–1.20 (6 H, m), 0.88–0.91 (3 H, t), 0.76–0.80 (6 H, m). ^{13}C NMR (DMSO-d_6) δ 14.14, 18.63, 19.69, 22.20, 27.35, 27.67, 28.12, 32.76, 48.52, 51.81, 62.25, 67.91, 78.91, 126.18, 127.58, 128.17, 128.68, 130.28, 130.47, 130.97, 137.23, 139.59, 141.05, 162.37, 170.96, 173.81; ESIMS: m/z calcd. [M+]: 478; found: 479 [M + H+]. HRMS (ESI): *m/z* calcd. [M+]: 478; found: 479.17 [M + H+].

2-[(2′-Cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric Acid Methyl Ester (17)

Phosphorus oxychloride (0.64 g, 4.18 mmol) was added dropwise to a solution of compound 2-{[2′-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-ylmethyl]-pentanoyl-amino}-3-methyl-butyric acid methyl ester (**16**) (1 g, 2.09 mmol) in dry pyridine (5 ml) at 0°C. The resulting solution was stirred at 85°C (bath temperature under nitrogen for 14 h and, after being cooled to room temperature, was poured into a cold saturated solution of sodium carbonate (100 ml). After being cooled to room temperature, the mixture was quenched by addition of water, and the resulting emulsion was extracted with ethyl acetate. The combined organic phases were washed with water, 10% aqueous cupric sulfate solution, and brine. The solution then was dried over anhydrous magnesium sulfate, filtered, concentrated under vacuum, and purified by column chromatography (SiO_2, ethyl acetate/hexane 3:7), yielding compound 2-[(2′-cyano-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid methyl ester (**17**)[11] as a yellow oil (0.75 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.17–7.86 (m, 8 H), 4.53–4.87 (m, 2 H), 4.13–4.18 (m, 1 H), 3.25–3.33 (d, 3 H), 2.24–2.35 (m, 2 H), 2.00–2.13 (m, 1 H), 1.41–1.53 (2 H, m), 1.10–1.31 (2 H, m), 0.86–1.08 (3 H, m), 0.68–0.79 (6 H, m). ^{13}C NMR (DMSO-d_6) δ 14.16, 18.45, 19.59, 22.21, 27.56, 32,76, 48.39, 52.07, 62.17, 65.09, 110.46, 119.03, 126.72, 127.54, 128.51, 128.63, 130.66, 134.22, 136.86, 139.19, 144.72, 170.59, 174.13; ESIMS: m/z calcd. [M+]: 406; found: 407 [M + H+], 429 [M + +Na]. HRMS (ESI): m/z calcd. [M+]: 406; found: 407.06 [M + H+], 429.04 [M + + Na].

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