A Convenient and Practical Synthesis of Olmesartan Medoxomil Methyl Ether

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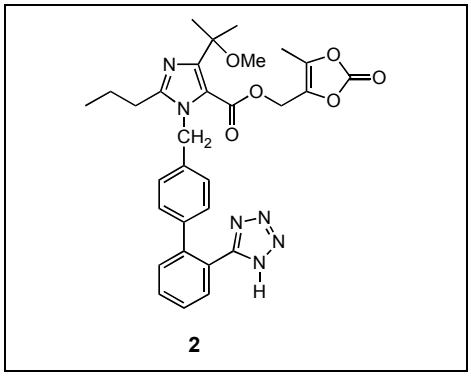

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Synthesis of Olmesartan medoxomil methyl ether (**2**), a potential impurity of Olmesartan medoxomil (**1**), an angiotensin II receptor blockers is reported for the first time.

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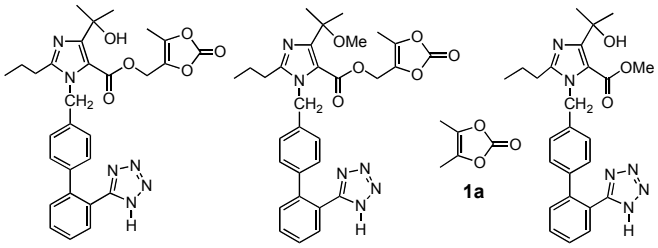
INTRODUCTION

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are known to be effective in treating hypertension and heart failure. Angiotensin II receptor blockers (ARBs) have emerged as an alternative way of blocking the rennin-angiotensin-aldosterone system (RAAS) and have been used in clinical practice since 1995 [1,2].



1 **2** **1a** **1b**

There are about seven ARBs in clinical practice, of which olmesartan medoxomil (**1**) is the newest agent in this class. It is a potent angiotensin II receptor antagonist that exhibits selective and potent antagonistic activity to AT_1 subtype [3]. It is a prodrug that is hydrolyzed during absorption and used in the treatment and prophylaxis of hypertension, including diseases of heart and circulatory system. Olmesartan medoxomil (**1**) lowers the blood pressure and improves the blood circulation by dilating blood vessels [4]. In general, the synthesis of **1** involves the coupling of substituted imidazole and substituted biphenyl methylene bromide [5]. However, the synthesis of **1** is always accompanied with the formation of the olmesartan medoxomil methyl ether (**2**) as a major impurity in the final product along with other minor impurities [6]. Impurity profiling of an Active Pharmaceutical Ingredient (API) involves isolation and characterization of the potential impurity by available analytical techniques. Synthesis of the impurity is always desirable for further confirmation of the proposed structure. To the best of our knowledge, no literature report is available for the synthesis of **2**. Therefore, a simple and convenient synthesis of **2** is essential to further confirm the structure of the impurity. This also provides an easy source to generate required quantity of the impurity for further batch analysis and regulatory needs. Hence we report a facile and efficient synthesis of **2** in good yield.

RESULTS AND DISCUSSION

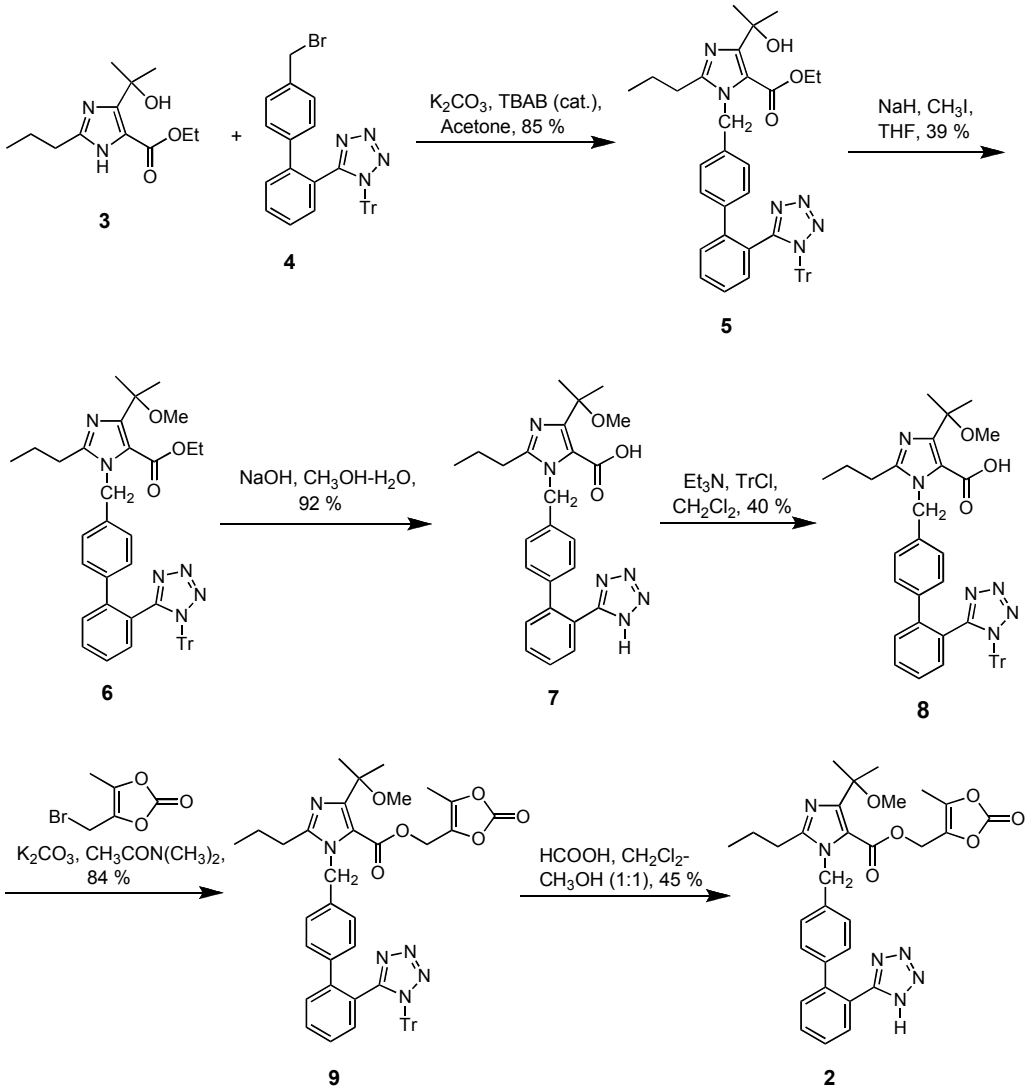
As **2** is a methyl ether derivative of **1**, attempts to methylate **1** with methyl iodide and NaH was not led to the formation of desired product **2** but the cleavage of ester bond was observed to give 4,5-dimethyl-2-oxo-1,3-dioxolene (**1a**) and methyl ester of carboxylic acid (**1b**). Similarly, the methylation of tritylated derivative of **1** with methyl iodide and NaH was also not successful and resulted in the formation of **1a** and **1b** along with the formation of **1** in minor quantities due to the detritylation.

Since the above attempts to synthesize **2** from **1** by direct methylation were unsuccessful, an alternative strategy to prepare **2** would be coupling of suitable alkylimidazole derivative with trityl protected biphenyl

derivative **(4)** followed by the methylation. Other strategy for preparing **2** is by *o*-methylation of **3** and followed by coupling with **4**. However, the *o*-methylation of **3** with MeI was unsuccessful. On the other hand protection of substituted imidazole **(3)** with BOC anhydride or trityl chloride to minimize the N-methylation of imidazole and to facilitate the *o*-methylation was also not successful. Several impurities were observed in case of BOC anhydride protection whereas no protection was observed in case of trityl protection.

Failure of these strategies prompted us to look for an alternative route for *o*-methylation. Accordingly, it was planned to do the coupling of the imidazole (**3**) with the bromo biphenyl moiety (**4**) followed by *o*-methylation, ester hydrolysis, introduction of the 4,5-dimethyl-2-oxo-1,3-dioxolene moiety and finally deprotection of trityl group to afford the desired compound **2**. As decided, 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-ethylcarboxylate **3** [7] was coupled with 4-{(2-trityltetrazol-5-yl)-phenyl}-benzyl bromide **4** [8] using potassium carbonate in acetone, and the product was crystallized to give **5** [9] in 85 % yield. This method has advantages over the reported method [9] where dimethyl acetamide or DMF was used and the product was isolated by column chromatography with low yield. Methylation of **5** with methyl iodide and sodium hydride was successful however the yields were low (39 %). Base hydrolysis of **6** was expected to liberate the acid. However, unusual detritylation of the base-stable trityl group occurred preferentially under basic condition and no ester hydrolysis was observed even with two equivalents of NaOH/ methanol in refluxing condition. Hydrolysis in the presence of more equivalents of base (9 equiv.) afforded the detritylated acid **7** in almost quantitative yield. Tritylation of **7** proceeded smoothly to **8** with moderate yield which on further coupling with 4-bromomethyl-5-

Scheme



methyl-2-oxo-1,3-dioxolene [10] in presence of potassium carbonate in dimethyl acetamide formed **9** in good yield. Finally, detritylation of **9** with formic acid in dichloromethane-methanol (1:1) at 40°C gave crude **2**, which was further purified by column chromatography and followed by recrystallisation in n-pentane to yield **2** as a white solid in 45 % yield.

In summary, a concise and practical route to olmesartan medoxomil methyl ether **2** was achieved, which will be helpful in the gram scale synthesis of this important impurity. In addition, the synthesis and characterization of compounds **6**, **7**, **8** and **9** are reported first time and some of them could be potential impurities of olmesartan medoxomil.

EXPERIMENTAL

Proton NMR spectra were obtained on a Bruker spectrometer with TMS as internal standard. Melting points were determined with a Buchi B-545 apparatus and are uncorrected. Mass spectra were obtained using Agilent 1200 series LCMSD/VL. IR spectra were taken on a Perkin-Elmer FT/IR 100 spectrometer and were run as KBr dispersion. Elemental analyses were performed on a Perkin Elmer 2400 series II CHNS/O analyzer. Thin layer chromatography was conducted on Merck Silica Gel 60 F_{254} plates. Column chromatography was performed using silica gel (230-400 mesh) procured from Sd-fine Chemical, India.

Ethyl-4-(1-hydroxymethylethyl)-2-propyl-1-{4-(2-trityl-tetrazol-5-yl)phenyl}phenylmethylimidazole-5-carboxylate (5). To a solution of 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-ethylcarboxylate (**3**) [7] (50 g, 0.208 mole) in acetone (500 mL) was added 4-((2-trityltetrazol-5-yl)-phenyl)-benzyl bromide (**4**) [8] (115.9 g, 0.208 mole), potassium carbonate (57 g, 0.413 mole) and tetrabutylammonium bromide (cat) at ambient temperature. The resulting mixture was heated at reflux for 16 hours. The reaction was cooled to room temperature, filtered and washed with acetone (100 mL). The combined filtrate and washings were concentrated under reduced pressure and the residue partitioned between ethyl acetate (2 × 200 mL) and water (2 × 200 mL). The combined ethyl acetate layer was dried over anhydrous sodium sulfate and recovered at reduced pressure. To the residue 500 mL isopropyl alcohol was added and the resulting solution was stirred at ambient temperature for 12 hours. The solids were filtered, washed with isopropyl alcohol (100 mL) and dried in air at 40-45°C for 12 hours to afford **5** [9] as a white powder (126 g, 85 %). M.P. 161°C; IR (KBr): 3407, 3056, 2977, 2935, 1961, 1702, 1666, 1603, 1470, 1290, 1177, 1033, 881, 756, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 0.84-0.91 (t, *J* = 13.6 Hz, 3H), 1.04-1.11 (t, *J* = 13.6 Hz, 3H), 1.64 (s, 6H), 1.70-1.82 (m, 2H), 2.48-2.55 (t, *J* = 14.4 Hz, 2H), 4.07-4.17 (q, *J* = 13.6 Hz, 2H), 5.35 (s, 2H), 6.07-6.74 (m, 2H), 6.94-6.97 (m, 6H), 7.08-7.11 (m, 2H), 7.26-7.47 (m, 12H), 7.85-7.88 (m, 1H). ESI (APCI)-MS: m/z 717 (M+1).

Ethyl-4-(1-methoxy-1-methylethyl)-2-propyl-1-{4-(2-trityl-tetrazol-5-yl) phenyl}phenylmethylimidazole-5-carbox-ylate (6). To a stirred suspension of sodium hydride (3.0 g, 0.075 mole) in THF (100 mL) was slowly added drop wise a solution of **5** (25 g, 0.034 mole) and methyl iodide (6.5 mL, 0.104 mole) in THF (100 mL) at 0°C. The reaction was slowly warmed to room temperature and stirred for further 6 hours. The reaction was then cooled to 0°C and water (30 mL) was added carefully to the mixture and extracted twice with ethyl acetate (2 × 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to give crude **6**, which was chromatographed on silica gel using 20% ethyl acetate in hexane to afford pure **6** as a white solid (10 g, 39 %). M.P. 134°C; IR (KBr): 3650, 3053, 2966, 1964, 1902, 1816, 1721, 1599, 1547, 1499, 1472, 1424, 1272, 1145, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 1.02-1.09 (t, *J* = 14.4 Hz, 3H), 1.35-1.43 (t, *J* = 14.4 Hz, 3H), 1.70-1.82 (m, 2H), 1.84 (s, 6H), 2.66-2.74 (t, *J* = 15.2 Hz, 2H), 3.31 (s, 3H), 4.29-4.40 (q, *J* = 14.4 Hz, 2H), 5.46 (s, 2H), 6.93-6.97 (d, *J* = 16 Hz, 2H), 7.12-7.16 (d, *J* = 14 Hz, 6H), 7.29-7.25 (d, *J* = 16.4 Hz, 2H), 7.41-7.56 (m, 12H), 7.63-7.68 (m, 1H). ESI(APCI)-MS: m/z 731 (M+1). *Anal* Calcd. for $C_{46}H_{46}N_6O_3$: C, 75.59; H, 6.34; N, 11.50. Found: C, 75.41; H, 6.29; N, 11.53.

4-(1-Methoxy-1-methylethyl)-2-propyl-1-{4-(2-tetrazol-5-yl) phenyl}phenylmethylimidazole-5-carboxylic acid (7). To a solution of **6** (5 g, 0.011 mole) in methanol (50 mL) was slowly added a saturated solution of sodium hydroxide (3.6 g, 0.09 mole) at ambient temperature and the mixture was heated at reflux for 16 hours. It was then cooled to room temperature and the solvents were removed under reduced pressure. The residue was dissolved in water (30 mL) and washed twice with ethyl acetate (2 × 100 mL). The aqueous layer was cooled to 5-10°C, acidified to pH 3-4 with dilute hydrochloric acid and extracted with ethyl acetate (2 ×100 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and the solvent was evaporated *in vacuo* to give **7** as a colorless solid (2.9 g, 92 %). M.P. 183-4°C; IR (KBr): 2975, 1935, 1706, 1624, 1460, 1365, 1154, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 0.90-0.97 (t, *J* = 14.4 Hz, 3H), 1.60 (s, 6H), 1.65-1.73 (m, 2H), 2.64-2.70 (m, 2H), 2.58 (s, 3H), 5.66 (s, 2H), 6.92-6.96 (d, *J* = 16 Hz, 2H), 7.07-7.11 (d, *J* = 16.4 Hz, 6H), 7.45-7.60 (m, 2H), 7.67-7.70 (m, 1H). ESI (APCI)-MS: m/z 459 (M-1). *Anal* Calcd. for $C_{25}H_{28}N_6O_3$: C, 65.20; H, 6.13; N, 18.25. Found: C, 65.43; H, 6.12; N, 18.27.

4-(1-Methoxy-1-methylethyl)-2-propyl-1-{4-(2-trityltetraz-ol-5-yl)phenyl}phenylmethylimidazole-5-carboxylic acid (8). To a stirred solution of **7** (26 g, 0.056 mole) in dichloromethane (200 mL), triethylamine (11.3 g, 0.111 mole) was added at room temperature. To this solution was added slowly drop wise a solution of trityl chloride (28.2 g, 0.101 mole) in dichloromethane (60 mL) and the resulting mixture was stirred for 5 hours at the room temperature. Water (520 mL) was added to the reaction mixture and the organic layer was separated, dried over anhydrous sodium sulphate, filtered and the solvent evaporated *in vacuo* to give crude **8**. Purification by column chromatography on silica gel using 35 % ethyl acetate in hexane afforded **8** as an off-white solid (16g, 40 %). M.P. 139 °C; IR (KBr): 2971, 1630, 1495, 1448, 1362, 1188, 1005, 759, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 0.83-0.90 (t, *J* = 14.4 Hz, 3H), 1.45-1.53 (m, 2H), 1.56 (s, 6H), 2.35-2.42 (m, 2H), 3.35 (s, 3H), 5.57 (s, 2H), 6.80-6.84 (d, *J* = 14.8 Hz, 2H), 6.91-6.95 (d, *J* = 14 Hz, 6H), 7.04-7.08 (d, *J* = 15.2 Hz, 2H), 7.28-7.45 (m, 12H), 7.85-7.89 (m, 1H). ESI (APCI)-MS: m/z 703 (M+1). *Anal* Calcd. for $C_{44}H_{42}N_6O_3$: C, 75.19; H, 6.02; N, 11.96. Found: C, 75.22; H, 6.03; N, 11.93.

4-(1-Methoxy-1-methylethyl)-2-propyl-1-{4-(2-trityltetra-zol-5-yl)phenyl}phenylmethylimidazole-5-carboxylic acid-5-methyl-2-oxo-[1, 3]-dioxolene-4-yl-methyl ester (9). To a stirred solution of **8** (17.5 g, 0.025 mole) in dimethyl acetamide

(150 mL) anhydrous K_2CO_3 (8.6 g, 0.062 mole) was added under nitrogen atmosphere at room temperature. A solution of 4-bromomethyl-5-methyl-2-oxo-1, 3-dioxolene [10] (5.8 g, 0.030 mole) in dimethyl acetamide (25 mL) was then added drop wise slowly and the resulting mixture was stirred at the same temperature for 5 hours. The mixture was filtered through hyflo bed and washed with ethyl acetate (100 mL). The combined filtrate and washings were added to water (525 mL) and extracted with ethyl acetate (2 × 450 mL). The ethyl acetate layer was separated, dried over anhydrous sodium sulphate and filtered. The solvents were concentrated under reduced pressure to afford crude **9**, which was purified by column chromatography on silica gel using 32 % ethyl acetate in hexane to give **9** as viscous oil (17 g, 84 %). IR (KBr): 2931, 1823, 1730, 1493, 1447, 1283, 1226, 1153, 748, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 0.84-0.92 (t, *J* = 14.8 Hz, 3H), 1.62 (s, 6H), 1.54-1.71 (m, 2H), 2.09 (s, 3H), 2.37-2.45 (t, *J* = 14.8 Hz, 2H), 3.08 (s, 3H), 4.78 (s, 2H), 5.26 (s, 2H), 6.71-6.75 (d, *J* = 16.4 Hz, 2H), 6.94-6.98 (d, *J* = 14 Hz, 6H), 7.06-7.10 (d, *J* = 16 Hz, 2H), 7.30-7.44 (m, 12H), 7.85-7.88 (m, 1H). ESI (APCI)-MS: m/z 815 (M+1). *Anal* Calcd. for $C_{49}H_{46}N_6O_6$: C, 72.22; H, 5.69; N, 10.31. Found: C, 72.18; H, 5.70; N, 10.28.

4-(1-Methoxy-1-methylethyl)-2-propyl-1-{4-(2-tetrazol-5-yl)phenyl}phenylmethylimidazole-5-carboxylic acid-5-methyl-2-oxo-[1,3]-dioxolene-4-yl-methyl ester (2). Formic acid (30 mL) was added to a solution of **9** (15 g, 0.012 mole) in dichloromethane-methanol (1:1, 300 mL) and heated to 40°C for 6 hours. The solution was cooled to room temperature and the solvents were removed under reduced pressure. The residue was taken in water (150 mL) and extracted with ethyl acetate (2 × 375 mL). The combined organic extracts were washed with 10 % $NaHCO_3$ solution (75 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvents under reduced pressure at 38°C afforded crude **2** which on purification by column chromatography on silica gel using 22 % acetone in hexane afforded solid which on recrystallisation in *n*-pentane afforded pure **2** as a white solid (4.7 g, 45 %). M.P. 72°C; IR (KBr): 2966, 1822, 1711, 1465, 1390, 1227, 1191, 1135, 1054, 1007, 769 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 400 MHz δ 0.87-0.95 (t, *J* = 14.8 Hz, 3H), 1.48 (s, 6H), 1.55-1.70 (m, 2H), 2.11 (s, 3H), 2.35-2.42 (t, *J* = 14.8 Hz, 2H), 3.01 (s, 3H), 4.89 (s, 2H), 5.33 (s, 2H), 6.79-6.83 (d, *J* = 16.4 Hz, 2H), 7.09-7.14 (d, *J* = 16.4 Hz, 2H), 7.42-7.57 (m, 3H), 7.86-7.90 (dd, *J* = 2.8 and 15.2 Hz, 1H). ESI (APCI)-MS: m/z 573 (M+1). *Anal* Calcd. for $C_{30}H_{32}N_6O_6$: C, 62.93; H, 5.63; N, 14.68. Found: C, 62.88; H, 5.64; N, 14.71.

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