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Novel synthesis of ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H -imidazole-5-carboxylate: A key intermediate of olmesartan

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ABSTRACT

A novel method for synthesis of ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5 -carboxylate(2), a key intermediate of Olmesartan was reported. The compound 2 was synthesized from starting material ethyl oxalate (4) and ethyl chloroacetate (5) by three steps. The final compound was purified by simple acid-base treatment to get a product with 99.5% HPLC purity.

Key words: Olmesartan; ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H -imidazole-5-carboxylate; ethyl chloroacetate; ethyl oxalate; butyramidinium

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INTRODUCTION

Olmesartan medoxomil (**1**) is a nonpeptide angiotensin II-type I receptor (AT1) antagonist with greater affinity for this receptor than other drugs in this class[1].A key step in the published syntheses of **1** is the regioselective N-alkylation of ethyl 4-(2-hydroxypropan-2-yl)-2-propyl -1H-imidazole-5 -carboxylate (**2**) using 4-bromomethyl-2,2 -biphenyltetrazole (**3**)(Scheme 1)[2,3]. As a key intermediate for **1**, there has been considerable interest in the development of economically viable and technically feasile syntheses of compound **2**. In the past decade, most documents reported the synthesis of compound **2** from diaminomaleonitrile and trimethyl orthobutyrate via condensation, hydrolyzation, esterifcation, Grignard reaction in 62.7% overall yield[4]. This procedure is not commercially viable because of the diaminomaleonitrile, which is toxic, expensive starting material. Later , Yu et al. employ tartaric acid as starting material via nitration, cyclization, esterifcation, Grignard reaction to synthesis of compound **2** in 60.1% overall yield[5,6]. This procedure is not suitable for commercial exploitation because of the use of high corrosive HNO_3/H_2SO_4 . In another approach, compound **2** was synthesized from o-phenylenediamine and butanoic acid via condensation, oxidation, esterifcation, Grignard reaction in 32.2% overall yield[7,8]. However, this procedure is not practical for large-scale production because of the disadvantages of high temperature in oxidation step, low total yield and producing byproduct in oxidation reaction. Here we developed a novel synthesis method for intermediate 2 from diethyl oxalate (**4**) and ethyl chloroacetate (**5**) or ethylacetate (**6**) as more cheaper starting material. The synthesis strategy was outlined in Scheme 2.

EXPERIMENTAL SECTION

3.1 Diethyl 2-chloro-3-oxosuccinate(8)

Sodium metal(2.4g, 104mmol) was dissolved in ethanol (30mL) and the solution cooled to 0 ^{o}C. To the solution was added ethyl oxalate (14g, 96mmol), and added dropwise ethyl chloroacetate (11g, 90mmol) at 0-5 ^{o}C for 2h. After addition , the mixture was stirred at room temperature for 24h and then concentrated under vacuum. The salt obtained was dissolved in ice-cold water(20mL) before adjustment of pH to 3 by addition of dilute hydrochloric acid.

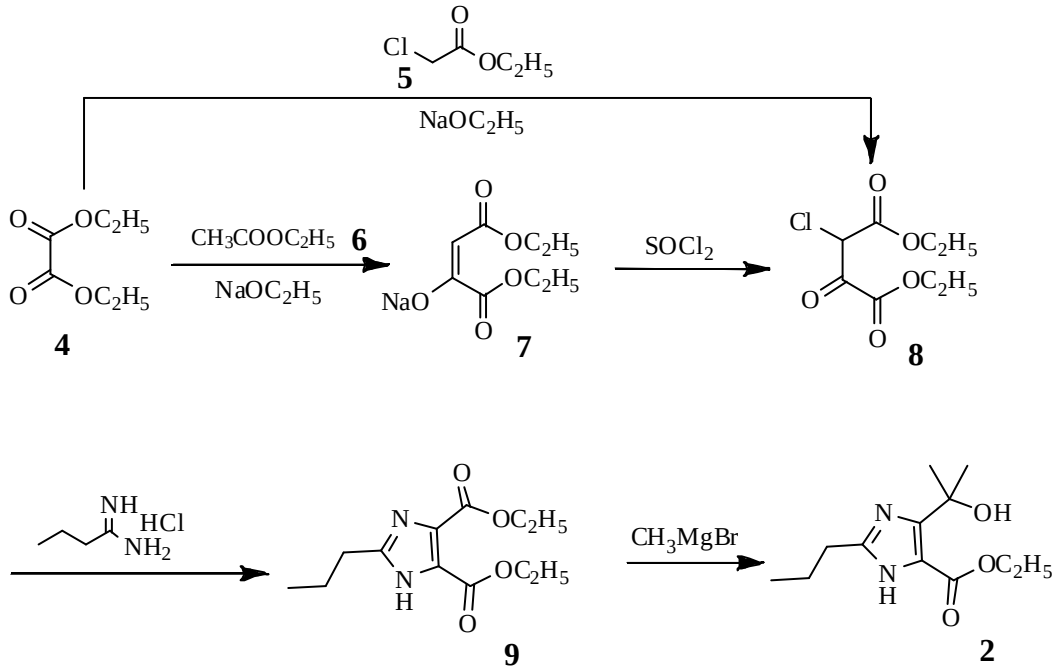
The mixture was extracted with EtOAc (20mL×3), and the combined ethylacetate solutions were dried and evaporated. Distillation of the product in a vacuum gave diethyl 2-chloro-3-oxosuccinate as a pale yellow liquid (11.9g, 59.5%).

3.2 Diethyl 2-propyl -1H –imidazole -4,5 –dicarboxylate (9)

Butyramidinium chloride(4g, 32.6mmol)was dissolved in absolute ethanol (20mL) and Et_3N(4.6mL) at room temperature. Diethyl 2-chloro -3-oxosuccinate(8g,36mmol) was added to the solution at room temperature over a 20min period. The reaction was stirred at room temperature for 1h then stirred at 60-70 ^oC for 5h. After evaporating the solvents under vacuum, water(40mL) was added to the residue. The mixture was extracted with EtOAc (30mL×3), and the combined ethylacetate solutions were dried and evaporated under reduced pressure gave the desired product as a white solid (**9**)(6.5g, 71%).m.p.:82-84 ^oC (lit.[4]m.p.:84-86 ^oC).

3.3 Ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1H -imidazole-5-carboxylate(2)

To a stirred solution of MeMgBr (2mol/L) in THF(120mL,0.24mol) was added a solution of diethyl 2-propyl-1H-imidazole-4,5-dicarboxylate (10g,0.04 mol) in CH_2Cl_2 (30mL) at 0-10 ^oC under N_2.The mixture was stirred at 15 ^oC for 1h and then diluted with EtOAc (100mL) and aqueous NH_4Cl (60mL) at 0 ^oC, successively. The organic phase was sepatated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a syrup. To this syrup were added dilute hydrochloric acid (10% w/w, 100mL) and active charcoal (1g). The mixture was stirred at 50 ^oC for 30min and filtered to remove active charcoal. The filtrate was cooled to 0 ^oC before adjustment of the pH to 7 by addition of 10% NaOH and solidified at -5 ^oC. The solid (ice) was melted at room temperature and the precipitate was filtered, washed with water, and dried under vacuum to give a white solid (7.8g, 82.6%); m.p.: 100-102 ^oC (lit.[4]m.p.:101-102 ^oC). 99.5%HPLC purity. The ^{1}HNMR and Mass spectral are in complete agreement with the literature values[4,5].



Scheme 2.

RESULTS AND DISCUSSION

Diethyl-2-substitute-1,3-thiazole-4,5-dicarboxylate can be synthesized by thioamide and diethyl 2-chloro-3-oxosuccinate(**8**)[9,10]. Analysed on this reaction made us realize that diethyl 2-propyl-1H-imidazole-4,5-dicarboxylate(**9**) also can be synthesized by butyramidinium and compound **8**. There were two methods synthetic toward the compound **8** (Scheme 2). ①Compound **8** is prepared by ethyl chloroacetate (**5**) dropwise to a solution of ethyl oxalate (**4**) and ether containing alcohol-free sodium ethoxide at room temperature and maintaining the reaction mixture for 24h[11,12]. ②Compound **8** is prepared by sulfuryl chloride dropwise to a solution of formic acid、chloroform and sodium salt of diethyl oxalacetate(**7**) at 20-30 ^oC for 2h and reacting at 40 ^oC for 5h[13]. Compound **7** is generally prepared[14] by EtOAc(**6**)、ethyl oxalate (**4**) and absolute

ethanol containing sodium ethylate at 5 ^{o}C for 4h and refluxing for 0.5h to get a paste pale-yellow mass. Our repeated attempts on those reactions made us realize that the first method was priority selection and the ether solvent was not necessary in this method.

Thus, ethyl chloroacetate (**5**) was added dropwise to a solution of ethyl oxalate (**4**) and absolute ethanol containing sodium ethylate at 0-5 ^{o}C for 3h and stirring at room temperature for 24h to get a cloudy white mass. After evaporation the solvents under vacuum, chloroform was added to the salt obtained and the solution was acidified with dilute hydrochloric acid to get compound **8**. Compound **8** was then reacted with butyramidinium in EtOH by condensation to produce diethyl 2-propyl-1H -imidazole-4,5-dicarboxylate(**9**). Then compound 9 was reacted with CH_3MgBr by Grignard reaction to give ethyl 4-(2-hydroxypropan-2-yl) -2-propyl-1H -imidazole-5-carboxylate (**2**). The product was characterized ^{1}HNMR and Mass spectral analysis and is in agreement with literature data[4,5].

CONCLUSION

The above report describes a rapid, practical and commercially viable process for the preparation of ethyl 4-(2–hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylate. The procedure is attractive and speedy due to fewer steps、simpler operation、mild reaction conditions and lower cost.

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