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Research Article

A Novel and Efficient Synthesis of Intermediates for the Preparation of Fexofenadine

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An efficient and environmentally friendly synthetic approach for the preparation of fexofenadine was developed. The method involves hydrogenation and oxygenation reaction and has good atom utilization, all the starting material is nontoxic.

1. Introduction

Fexofenadine (**4**), the carboxylic acid metabolite of terfenadine and the actual pharmacologically active compound [1–3], is a selective histamine H1 receptor antagonist, clinically effective in the treatment of seasonal allergic rhinitis, and chronic idiopathic urticaria as a first-line therapeutic agent [3–5]. Several synthetic routes to fexofenadine have been reported [6–15]. However, a review of the literature, including patents, indicated the absence of both environmentally benign and relatively low-cost method for its synthesis. A summary of known representative procedures is shown in Schemes 1 [14, 15] and 2 [16, 17], these methods utilize either reaction of poor regioselectivity or unwieldy and expensive reagents. Although, Scheme 2 [16, 17] is a relatively low-cost and convenient operation method and also solves the problem of purification caused by the formation of the ortho isomer (step 1, Scheme 2), the mercury byproduct is harmful and difficult to remove. In connection with our systematic studies on the process of fexofenadine, we have developed an environmentally friendly modified method for synthesis intermediates toward its preparation (Scheme 3).

Hydrogenation of alkyne **5** on a modified Lindlar catalyst system (5% $Pd/CaCO_3$ and a small amount of tertiary amine) to give alkene **7** (95% yield). Alkene **7** was obtainedinonly 70% yield if the commercial Lindlar catalyst obtained from the Catalysis Institute of Zhejiang University was used because of the production of saturate ester as a byproduct. Alkene **7** was subsequently oxidized to the methyl ester **6** with oxygen at room temperature, using the catalytic system of $Mn(OAc)_2$, $NaBH_4$, and Schiff-base ligand (**B**) [18, 19]; subsequently, hydrolysisofmethyl ester **6** with hydrochloric acid afforded fexofenadine **4**.

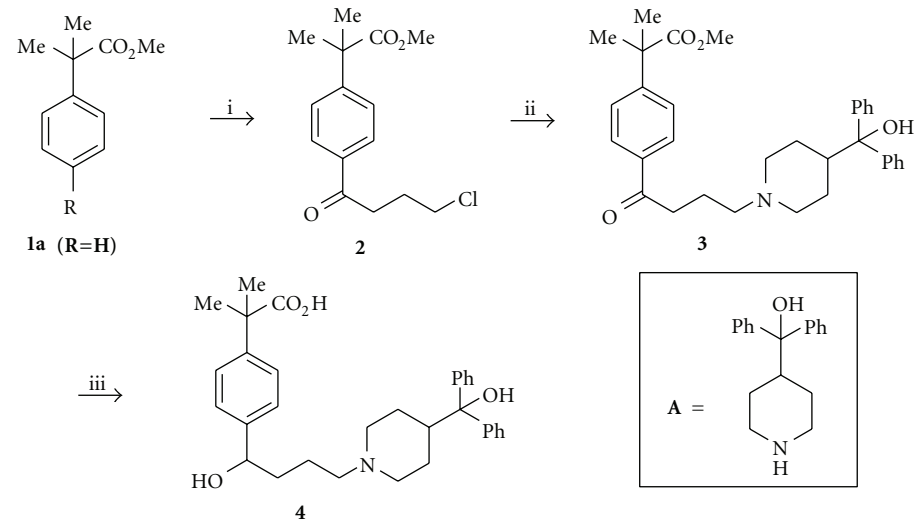
In summary, this synthesis has good atom utilization, the starting material is inexpensive and readily available commercially, the new method has the advantage of good yield and of being environmental benign. This procedure seems to be amenable to pharmaceutical manufacture.

2. Experimental Section

Melting points are uncorrected. Infrared spectra were obtained on an IR-408 instrument. ^1H NMR spectra were recorded on a Bruker 400 (400 MHz) instrument using $CDCl_3$ as the solvent with TMS as internal standard. All other chemicals were reagent grade.

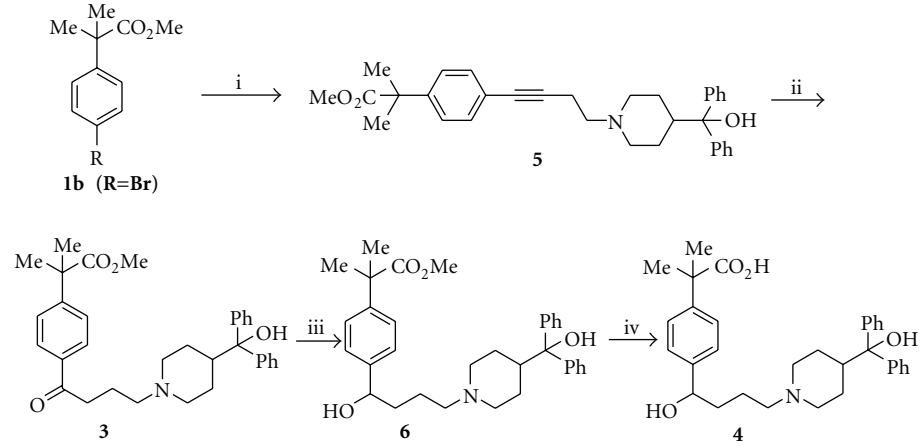
2.1. Synthesis of 4-{4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-butenyl}-α,α-dimethyl-benzeneacetic acid methyl ester (7)

A solution of compound **5** (4.45 g, 8.99 mmol) in 300 mL ethanol and 0.38 g of Lindlar catalyst (palladium:$CaCO_3$ 1:20) was added to a 500-mL autoclave under a nitrogen atmosphere, and quinoline (1.0 mL) was slowly added dropwise to the stirred mixture at 20–25°C. Subsequently,



(i) $Cl(CH_2)_3COCl$, $AlCl_3$ (ii) **A** (iii) NaOH, MeOH, then $NaBH_4$, EtOH

Scheme 1



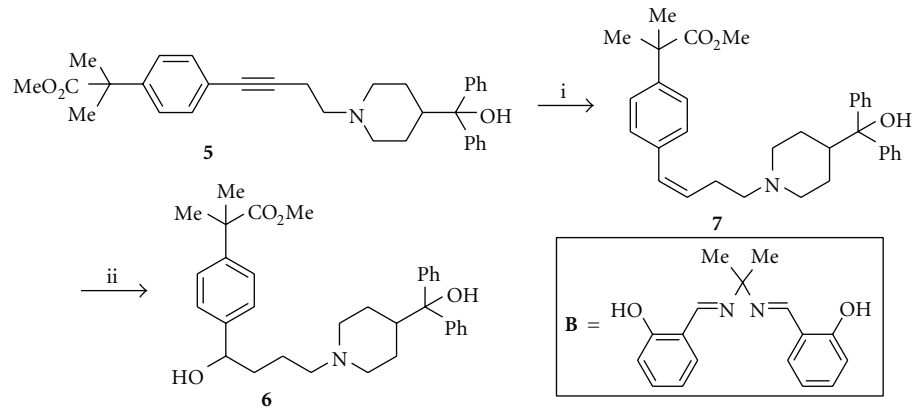
(i) $HC{\equiv}C(CH_2)_2OH$, MsCl, then **A** (ii) HgO (iii) $NaBH_4$ (iv) HCl

Scheme 2

hydrogen was introduced into the autoclave at a H_2 pressure of 0.2 Mpa, the reaction mixture was stirred under 0.2 MPa pressure of hydrogen at 30°C for 10 hours before releasing hydrogen, and then filtered by suction. The filtrate was concentrated to give 4.02 g (90% yield) of alkene **7** as a white solid, mp 118–123°C. IR: 3374, 3055, 2945, 1729, 1597, 1447, 1147 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.47 (d, 4H), 7.29–7.14 (m, 10H), 6.40 (d, 1H), 5.60 (m, 1H), 3.63 (s, 3H), 2.95 (d, 2H), 2.52–2.41 (m, 5H), 1.98–1.94 (m, 2H), 1.56 (s, 6H), 1.51–1.46 (m, 4H); ^{13}C NMR: δ 177.2, 146.1, 143.0, 136.0, 130.5, 129.3, 128.8, 128.3, 127.0, 126.2, 125.5, 79.5, 58.6, 54.1, 52.3, 46.3, 44.2, 26.6, 26.5, 26.4; MS (EI) *m/z*: 498 $[M + 1]^+$; HRMS (EI): $[M + 1]^+$ Calcd for $C_{33}H_{39}NO_3$: 498.3003. Found: 498.2999. Anal. Calcd for $C_{33}H_{39}NO_3$: C, 79.64; H, 7.90; N, 2.82. Found: C, 79.62; H, 7.93; N, 2.84.

2.2. Synthesis of 4-[1-Hydroxy-4-[4-(hydroxy-diphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl-benzeneacetic acid methyl ester (6)

$Mn(OAc)_2$ (0.11 g, 0.64 mmol), the Schiff-base ligand **B** [18, 19] (0.20 g, 0.64 mmol), and $NaBH_4$ (0.62 g, 16.18 mmol) were added to a stirred solution of compound **7** (4.02 g, 8.09 mmol) in 150 mL of a mixture of toluene and ethanol (1:1). The mixture was stirred at room temperature under oxygen pressure of 0.1 MPa for 4 hours, the progress of reaction was monitored by TLC. The ethanol was removed under reduced pressure and the organic layer was washed with water, dried over $MgSO_4$, and filtered under vacuum.



(i) H_2, 5% $PdCO_3$, quinoline, EtOH (ii) O_2, $Mn(OAc)_2$, then $NaBH_4$, **B**

Scheme 3

The filtrate was evaporated in vacuo to give crude product **6**, which was chromatographed over silica gel (1:5 hexanes-acetone, v/v) to give pure methyl ester **6** (3.65 g, 90%) as a white powder, mp 157-158°C. IR 3540, 3062, 2931, 2808, 1713, 1445, 1148 cm^{-1}; ^1H NMR($CDCl_3$): δ 7.51–7.13 (Ar, 14H), 4.59 (d, 1H), 3.15 (d, 1H), 2.98 (d, 1H), 2.50–2.40 (m, 4H), 2.17 (t, 1H), 2.00 (t, 1H), 1.90–1.48 (m, 13H); ^{13}C NMR: δ 177.2, 145.9, 144.0, 142.7, 127.9, 126.2, 125.6, 125.5, 79.0, 76.6, 58.6, 54.5, 53.1, 51.9, 46.0, 41.0, 39.5, 26.3, 25.8, 25.7; MS *m/z* 515(M^+). Anal. Calcd for $C_{33}H_{41}NO_4$: C, 76.86; H, 8.01; N, 2.72. Found: C, 76.88; H, 8.03; N, 2.69.

Acknowledgments

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