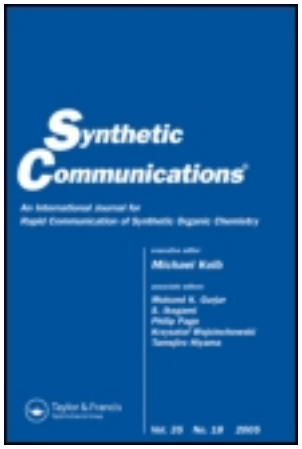

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NOVEL AND EFFICIENT METHOD FOR THE SYNTHESIS OF RACEMIC FEXOFENADINE

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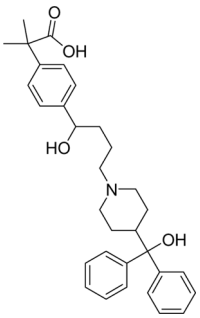
GRAPHICAL ABSTRACT



Abstract *Fexofenadine is a selective H_1-histamine receptor antagonist, which is an attractive alternative treatment for allergy symptoms. An efficient and environmentally friendly synthetic approach for the preparation of fexofenadine was developed from commercially available cumene. The method involves the Friedel–Craft's reaction, substitution, reduction, bromination, and the Grignard reaction.*

Keywords Fexofenadine; H_1-histamine receptor; histamine antagonists; tetrafenadine

INTRODUCTION

Histamine plays an important role in a variety of physiological processes. It regulates smooth muscle contraction, increases vascular permeability, stimulates gastric secretion, regulates the functions of the central nervous system, and modulates the regulation of cell proliferation and differentiation.[1] Nevertheless, histamine is also a potent mediator of inflammation and tissue remodeling and serves as a modulator in various autoimmune diseases (e.g., rheumatoid arthritis osteoarthritis and especially allergic diseases).[2,3] The biological effects of histamine are mediated via

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binding to four types of histamine receptors (H_1–H_4) expressed on various cell types. The binding of histamine to an H_1-receptor induces the progress of the allergic symptoms, and these are prevented using histamine H_1-receptor blockers in particular. This group of drugs, known as H_1-antihistamines, is used clinically as antiallergic and antiemetic drugs[4,5] and possesses anti-inflammatory and antiplatelet activities.[6,7]

Fexofenadine and terfenadine are selective H_1-histamine receptor antagonists that do not cause drowsiness. Fexofenadine is the carboxylic acid metabolite of terfanadine. It has been documented that terfenadine can cause severe cardiovascular side effects when used in conjunction with certain antifungal or antibacterial agents.[8] Racemic fexofenadine reportedly does not cause ventricular arrhythmias and is an attractive alternative for the treatment of allergy symptoms. Currently, it is marketed as Allegra. In contrast to their structural similarities, the synthetic route for terfenadine, which employs the Friedel–Crafts reaction to introduce the *para* substitution of the *tert*-butylphenyl ring, is not very efficient for the synthesis of fexofenadine. The acylation of ethyl 2-methyl-2–phenylpropanate with 4-chlorobutyryl acid chloride was reported and displayed the predominance of *meta* to *para* regio-isomer, and the required separation of isomers results in poor yield.[9] Other approaches were used to circumvent this lack of regioselectivity. Use of α 1,4-disubstituted phenyl ring like 2-(4-bromophenyl) acetic acid[10] and 2-(4-bromophenyl) acetonitrile[11] avoids the Friedel–Crafts reaction. Another strategy was depicted by Di Giacomo et al.[12] from a precursor where the carboxylic acid group replaced by alcohol function, reducing strongly the electron-withdrawing effect of acid. This approach ensured a better *para* regioselectivity of the Friedel–Craft's reaction, but fexofenadine was obtained in only 7% yield from 2-methyl-2-phenyl propyl acetate. Recently, a reported regioselective synthesis of fexofenadine employing a Pd (0)-catalyzed coupling of a terminal alkyne and an aromatic bromide, followed by sequential regio selective hydration of the triple bond, gives the ketone, utilizing HgO/H_2SO_4 as the reagents.[13–15]

RESULTS AND DISCUSSION

Several synthetic routes to fexofenadine have been reported.[16–25] However, a review of the literature, including patents, indicated the absence of methods both environmentally benign and relatively low-cost for its synthesis. Some methods utilize either reaction of poor regioselectivity or unwieldy and expensive reagents. Although some of them[26,27] are relatively lowcost and convenient and also solve the problem of purification caused by the formation of the ortho isomer, the mercury by-product 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 its synthesis (Scheme 1).

Herein, we report six steps involving inexpensive starting material, reagents, and nonhazardous solvents, which can be conveniently applied for industrial-scale synthesis. All the synthesised compounds were structurally characterized by infrared (IR), ^{1}H NMR, liquid chromatography/mass spectrometry (LC/MS), and elemental analysis. In the first step, aluminium chloride–catalyzed Friedel–Craft's acylation of cumene with 4-chlorobutyryl chloride in dichloromethane gives specifically *para*

product with 92% yield. The presence of butanone proton peaks in the ^{1}H NMR spectra confirms the formation of 4-chloro-1-(4-isopropyl phenyl)butan-1-one **(2)**. Cumene is a very cheap and commercially available starting material compared to 2-ethyl(4-formyl phenyl)propionate. 2-Ethyl(4-formyl phenyl)propanate was not suitable for bulk production. The second step involves the nucleophillic substitution reaction of azacyclconol with compound **2** in the presence of base potassium carbonate in xylene, and refluxing for 1 h gave the compound **3**. The reduction of compound **3** was carried out under very mild reaction condition at 0–5 °C by using sodium borohydride in methanol for 0.5 h, yielding 74% of compound **4**. The presence of an –OH proton peak in the ^{1}H NMR spectra confirms the formation of the product.

The –OH group protection was tried by trimethyl silyl chloride and acetylation, but we got better results with good yield by using *tert*-butyldimethylsilyl chloride (TBDMS) at 0 °C under a nitrogen atmosphere in *N,N*-dimethyl formamide for 10 h. The absence of –OH proton peak in the ^{1}H NMR spectra confirms the protection of –OH group in compound **5**. Bromination of compound **5** was done by using *N*-bromo succinimide in carbon tetrachloride in the presence of a catalytic amount of hydrogen peroxide for 4 h giving 85% yield (confirmed by LC/MS spectra). The obtained bromo compound **6** was treated with magnesium in tetrahydrofuran (THF) to give the Grignard product. The compound was subsequently quenched with dry ice followed by deprotection of TBDMS using tetra-*n*-butylammonium fluoride at room temperature, giving the targeted compound fexofenadine with 60% yield.

CONCLUSIONS

Fexofenadine is a selective H_1-histamine receptor antagonist, which is an attractive alternative for the treatment of allergy symptoms. In this novel method, the starting material is inexpensive and commercially available. The new method has the advantages of good yield and of being environmental benign. This procedure seems to be amenable to pharmaceutical manufacture.

MATERIALS AND METHODS

All analytical thin-layer chromatography (TLC) was performed with E. Merck silica-gel 60 F_{254} aluminum sheets and was visualized with ultraviolet (UV) light. The following mobile phases were employed for TLC: chloroform, methanol, hexane, and ethyl acetate in different ratios.

The instrumental techniques employed for the characterization of the newly synthesized compounds include ^{1}H NMR and mass spectroscopy. The details of instrumentation are briefly given.

^{1}H (400-MHz) spectra were recorded on dimethylsulfoxide (DMSO-d_6) solution in a 5-mm tube on a Bruker AMX 400 and 300 Fourier transform spectrophotometer (at SIF, Indian Institute of Science, Bangalore, India) with tetramethylsilane (TMS) as internal standard. The spectrophotometer was internally locked to the deuterium frequency of the solvent. Chemical shifts were recorded in parts per million (ppm) relative to TMS. Mass and purity were recorded on a LC–MSD-Trap-XCT instrument.

EXPERIMENTAL

Synthesis of 4-Chloro-1-(4-isopropyl phenyl)butan-1-one (2)

Aluminium chloride (4.67 g, 35.0 mmol) was added to 100 mL of methylene chloride containing 4-chlorobutyryl chloride (4.49 g, 31.8 mmol), with stirring in an ice bath at about −10 °C. Then the mixture was recooled to 5 °C, and 4.97 g (41.3 mmol) of cumene in methylene chloride were added. The reaction mixture was stirred at room temperature for 10 h. The reaction was monitored by TLC, and then mixture was poured into HCl–ice water and extracted with methylene dichloride. The extract was washed with sodium carbonate water, and saturated sodium chloride solution; dried over anhydrous sodium sulfate; and evaporated to give the title compound as 92% clean oil. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.14–1.25 (m, 6H, -CH_2), 2.02–2.10 (m, 2H, -CH_2), 2.90–2.99 (m, 1H, -CH), 3.13 (t, 2H, -CH_2), 3.69 (t, 2H, -CH_2), 7.36 (d, 2H, $J = 8.2$ Hz, Ar-H), 7.89 (d, 2H, $J = 8.2$ Hz, Ar-H). IR (KBr, cm^{-1}): 3083, 1872, 1693, 643. MS (ESI +ion) m/z: 225.2. Anal. cacld. for $C_{13}H_{17}OCl$: C, 69.48; H-7.62. Found: C, 69.31; H,7.39.

Synthesis of 4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-one (3)

A mixture of azacylonol (4.5 g, 16.8 mmol), 4-chloro-1-(4-isopropyl phenyl)butan-1-one (5.0 g, 84.7 mmol), and potassium bicarbonate in 15 mL water was stirred, and 30 mL xylene were added and refluxed for 12 h. Progress of the reaction was monitored by TLC, and then the mixture was filtered. The solvent xylene was removed. The resulting precipitate was collected and recrystallized from methanol to give compound **3** with 65% as white solid. Mp: 145–149 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.38–1.46 (m, 2H, -CH_2), 1.68–1.75 (m, 6H, (-CH_3)$_2$), 1.83 (t, 2H, -CH_2), 1.81–1.86 (m, 4H, (-CH_2)$_2$), 2.12 (m, 1H, -CH), 2.48 (m, 1H, -CH), 2.80 (m, 2H, -CH_2), 2.90–2.97 (m, 4H, -(CH_2)$_2$), 5.20 (s, 1H, -OH), 7.10 (t, 2H, Ar-H), 7.24 (m, 4H, Ar-H), 7.35 (d, 2H, Ar-H), 7.48 (d, 4H, $J = 6.0$ Hz, Ar-H), 7.84 (d, 2H, $J = 6.3$ Hz, Ar-H). IR (KBr, cm^{-1}): 3092, 2125, 1520, 1245, 1086, 1687. MS (ESI + ion) m/z: 456.4. Anal. calcd. for $C_{31}H_{37}NO_2$: C, 81.72; H-8.19; N,3.08. Found: C, 81.79; H, 8.23; N, 3.06.

Synthesis of 4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-ol (4)

4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-one (3.0 g, 6.5 mmol) in 20 mL of methanol was cooled in an ice bath, and $NaBH_4$ (1.8 g, 47.5 mmol) was added in portions. After 0.5 h, the reaction was monitored by TLC, and then the reaction mixture was concentrated to a solid. The product was extracted with ethyl acetate. The ethyl acetate layer was washed with sodium chloride solution and dried over anhydrous magnesium sulfate, and the organic solvent was evaporated in vacuum to give compound **4**. Yield: 74%. Mp: 120–123 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.16 (s, 6H, (-CH_3)$_2$), 1.38–1.43 (m, 2H, -CH_2), 1.52–1.54 (m, 2H, -CH_2), 1.80 (m, 2H, -CH_2), 2.09 (m, 1H, -CH), 2.25 (m, 1H, -CH), 2.42–2.49 (d, 4H, -CH_2), 2.77–2.90 (m, 4H, -CH_2), 4.41 (t, 1H, -CH), 5.21

(s, 1H, -OH), 5.32 (s, 1H, -OH), 7.19–7.25 (m, 10H, Ar-H), 7.46 (d, 4H, Ar-H). IR (KBr, cm^{-1}): 3087, 2114, 1532, 1238, 1080. MS (ESI + ion) m/z: 458.40. Anal. calcd. for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.07. Found: C, 81.63; H, 8.54; N, 3.05.

Synthesis of *tert*-Butyl(4-(4-(hydroxyldiphenylmethyl)piperidin-1-yl)-1-(4-isopropylphenyl)butan-1-oxy)dimethylsilane (5)

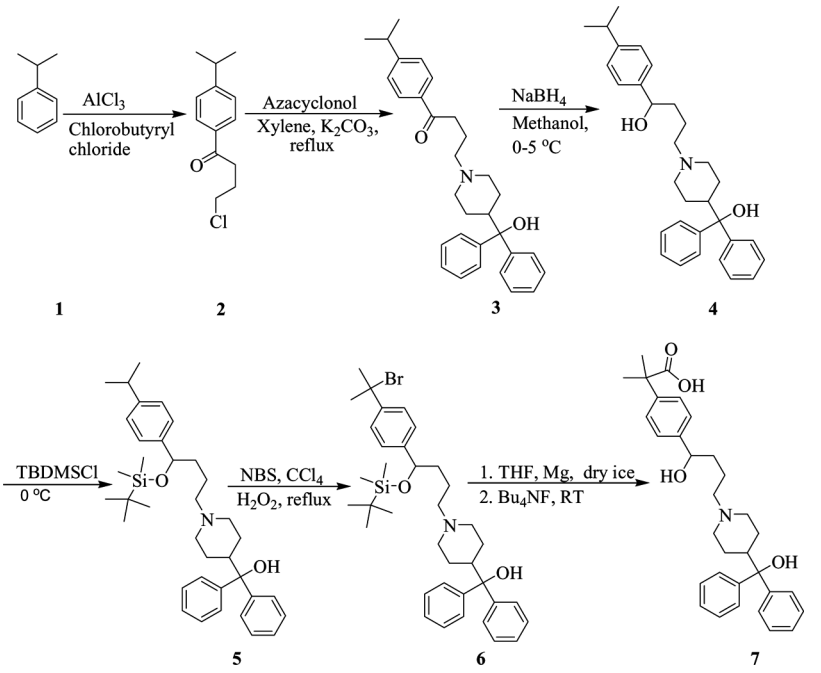
Solution of imidazole (2.0 g, 29.3 mmol) in *N,N*-dimethyl formamide and *tert*-butyl dimethylsilyl chloride (2.2 g, 14.6 mmol) were added at 0 °C under nitrogen to a solution containing **4** (2.79 g, 6.0 mmol) in 20 mL of *N,N*-dimethyl formamide. It was stirred for 15 min at 0 °C and 10 h at room temperature. The progress of the reaction was monitored by TLC. Then it was diluted with ether and washed with water, 5% sulfuric acid, and water. The organic layer was dried over anhydrous sodium sulfate, and the organic solvent was evaporated in a vacuum. The product was purified by column chromatography to give compound **5**. Yield: 90%. Mp: 94–96 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.063 (s, 6H, -$(CH_3)_2$), 0.89 (s, 9H, -$(CH_3)_3$), 1.25 (d, 6H, -$(CH_3)_2$), 1.59 (m, 4H, -$(CH_2)_2$), 2.10 (m, 1H, -CH), 2.36–2.45 (m, 6H, -$(CH_2)_3$), 2.50 (t, 2H, -CH_2), 2.74 (t, 2H, -CH_2), 3.23 (m, 1H, -CH), 4.24 (m, 1H, -CH), 5.15 (s, 1H, -OH), 7.16–7.26 (m, 10H, Ar-H), 7.53 (d, 4H, $J = 7.6$ Hz, Ar-H). Anal. cacld. for $C_{37}H_{52}NO_2BrSi$: C, 67.49; H, 7.95, N, 2.12. Found: C, 67.31, H, 7.83, N, 2.16. IR (KBr, cm^{-1}): 3081, 2128, 1541, 1246, 1098. MS (ESI + ion) m/z: 572.40. Anal. calcd. for $C_{37}H_{53}NO_2Si$: C, 77.70; H, 9.34; N, 2.45. Found: C, 77.74; H, 9.30; N, 2.38.

Synthesis of *tert*-Butyl(4-(4-(hydroxyldiphenylmethyl)piperidin-1-yl)-1-(4-(2-bromopropan-2-yl)phenyl)butan-1-oxy)dimethylsilane (6)

Compound **5** (5.0 g, 8.95 mmol) was dissolved in carbon tetrachloride, and *N*-bromo succinimide (1.91 g, 10.7 mmol) and a catalytic amount of hydrogen peroxide were added and refluxed for 4 h. The reaction was monitored by TLC. Finally, the product was purified by chromatography to give compound **6**. Yield: 85%. Mp: 88–92 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.085 (s, 6H, -$(CH_3)_2$), 0.85 (s, 9H, -$(CH_3)_3$), 1.16 (m, 6H, -$(CH_3)_2$), 1.37–1.43 (m, 2H, -CH_2), 1.19 (m, 4H, -$(CH_2)_2$), 1.77 (m, 2H, -CH_2), 2.14 (m, 2H, -CH_2), 2.50 (m, 4H, -$(CH_2)_2$), 2.84 (m, 1H, -CH), 4.65 (s, 1H, -CH), 5.20 (s, 1H, -OH), 7.09–7.15 (m, 2H, Ar-H), 7.17 (m, 4H, Ar-H), 7.24 (m, 4H, Ar-H), 7.48 (d, 4H, $J = 6$ Hz, Ar-H). IR (KBr, cm^{-1}): 3109, 2142, 1537, 1240, 1075. Anal. calcd. for $C_{37}H_{52}NO_2BrSi$: C, 68.44; H, 8.07; N, 2.16. Found: C, 68.36; H, 8.13, N-2.18.

Synthesis of 2-(4-(1-Hydroxy-4-(4-(hydroxydiphenylmethyl)-piperidin-1-yl)butyl)phenyl)-2-methylpropanoic acid (7)

Compound **6** (2.0 g, 3.08 mmol) was dissolved in tetrahydrofuran, and magnesium metal (0.12 g, 4.62 mmol) was added and stirred for 2 h in a nitrogen atmosphere. The mixture was transferred into another round-bottomed flask containing solid carbon dioxide and stirred for 4 h. Tetra-*n*-butylammonium fluoride[28] in



Scheme 1. Synthesis of racemic fexofenadine.

THF (2.68 mL, 9.24 mmol) was added into the reaction mixture and stirred for 4 h. The progress of the reaction was monitored by TLC. After completion, solvent was evaporated, and the product was quenched in the water, then washed with 10% hydrochloric acid and finally with water to give compound **7**. Yield: 60%. Mp: 188–191 °C. ^{1}H NMR (MeOD, 300 MHz) δ: 1.63 (s, 6H, -$(CH_3)_2$), 1.72–1.78 (m, 2H, -CH_2), 2.16 (t, 2H, -CH_2), 2.74 (m, 1H, -CH), 2.85 (m, 4H, -$(CH_2)_2$), 2.98 (m, 4H, -$(CH_2)_2$), 3.48 (d, 2H, -CH_2), 4.68 (s, 1H, -CH), 7.18 (t, 2H, Ar-CH), 7.28–7.38 (m, 8H, Ar-H), 7.51 (d, 4H, Ar-H). IR (KBr, cm^{-1}): 3542, 3060, 2935, 2803, 1718, 1441, 1145. MS (ESI + ion) m/z: 503.2. Anal. cacld. for $C_{32}H_{39}NO_4$: C, 75.59, H, 7.84, N, 2.80. Found: C, 76.48; H, 7.85; N, 2.45.

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