A SIMPLE AND STRAIGHTFORWARD SYNTHESIS OF ANTIHISTAMINIC DRUG CETIRIZINE

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ABSTRACT: The anti-histaminc drug cetirizine was synthesized in five linear steps with an overall yield of 50%. All the reactions were very clean and the isolation of products also very easy. Our synthetic strategy was applicable to large scale preparation of cetirizine.

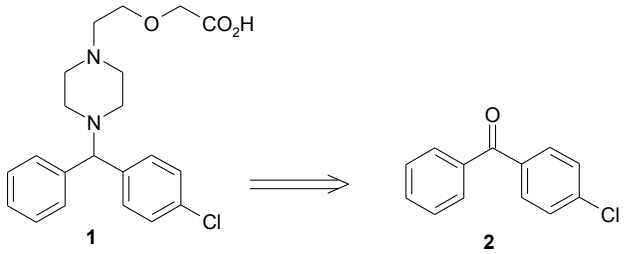
***Keywords*:** Chlorobenzophenone, sodium borohydride, Calcium chloride, piperazine, bromoethanol, 1-bromoacetic acid.

INTRODUCTION

Cetirizine a second-generation antihistamine, is a major metabolite of hydroxyzine and a racemic selective H_1 receptor inverse agonist used in the treatment of allergies, hay fever, angioedema, and urticaria.[1-4] The structural similarity of cetirizine to hydroxyzine and its derivation from piperazine, attribute similar adverse reactions and properties to other piperazine derivatives. Cetirizine crosses the blood-brain barrier only slightly, elimina ting the sedative side-effect common with older antihistamines. However it still causes mild drowsiness. It has also been shown to inhibit eosinophil chemotaxis and LTB4 release. Ceterizine is available as a generic drug in racemic form. It has one stereocenter and forms levo and dextro isomers. The levorotary enantiomer of cetirizine is more active and avaiable as levocetirizine. The pharmaceutical importance of this drug, was attracted many researchers[5-7] and most of the literature for the synthesis of cetirizine was in the form of patents.[8-12]As part of our ongoing program in design and synthesis of biologically active molecules,[13-18] herein we report a simple and efficient route for the synthesis of anti-histaminic drug Cetirizine.

RESULTS AND DISCUSSION

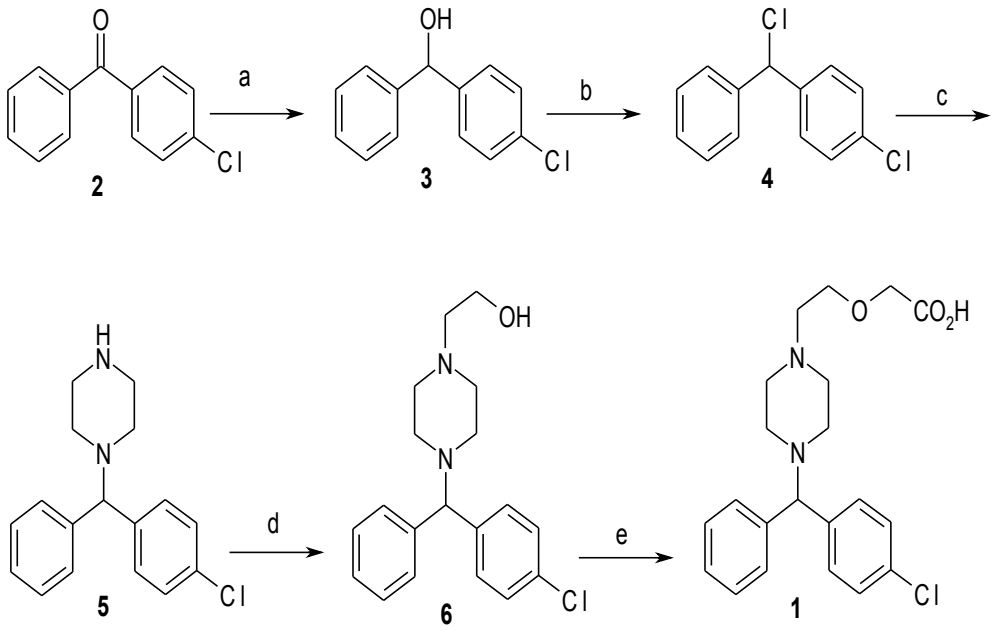
As shown in the retrosynthetic analysis (scheme 1), our synthetic strategy was started from commercially available chlorobenzophenone (2).



Scheme 1

The benzophenone compound **2** was treated with sodium borohydride in methanol to afford the corresponding product of (4-chlorophenyl) (phenyl) methanol (**3**) in quantitative yield. The product was confirmed by its spectral data, the ^{1}HNMR shows a broad singlet at δ 2.20 integrating for one proton of hydroxy group, a doublet at δ 5.75 integrating for one proton present on benzylic carbon and a multiplet at δ 7.25-7.35 integrating for 9 protons belongs to aromatic rings. The infra-red spectroscopy also shows a peak at υ 3360 cm^{-1} indicating the hydroxy group. Thus confirmed alcohol compound 3 was treated with calcium chloride and hydrochloric acid at 80-90 ^{0}C to afford the corresponding derivative of 1-chloro-4-[chloro(phenyl) methyl] benzene (4) in excellent yields. Thus obtained chloro product was confirmed by its ^{1}HNMR which shows a singlet at δ 6.05 integrating for one proton of benzylic carbon and the aromatic 9 protons appeared as a multiplet at δ 7.25-7.38. The chloro compound 4 was reacted with piperazine in presence of K_2CO_3 at tetrahydrofuran reflux to obtain the corresponding product of 1-[(4-chlorophenyl) (phenyl) methyl] piperazine (5) in excellent yields. The product 5 was confirmed by its spectral data, the ^{1}HNMR shows a broad singlet at δ 2.62 integrating for 4 protons, another broad singlet at δ 3.08 integrating for 4 protons are belongs to piperazine ring system, a singlet at δ 4.38 integrating for 1 proton of benzylic carbon and the aromatic protons appeared at as usual places. Thus confirmed piperazine compound **5** was reacted with 1-bromoethanol in presence of K_2CO_3 at acetonitrile reflux to obtained the corresponding derivative of 2-[4-((4-chlorophenyl) (phenyl) methyl) piperazin-1-yl] ethanol (6) in very good yields.

The above product 6 was confirmed by its spectral data. The ^{1}HNMR of which shows a broad singlet at δ 2.32-2.45 integrating for 5 protons belongs to piperazine four and one hydroxy, another broad singlet at δ 2.48-2.58 integrating for 6 protons belongs four from piperazine and two from aliphatic methylene, a triplet at δ 3.55 integrating for two protons of aliphatic methylene which was attached to hydroxy group, a singlet at δ 4.15 integrating for 1 proton of benzylic carbon and the aromatic protons appeared at as usual places.



Scheme 2

Reactions and reagents: (a) $NaBH_4$, methanol, 0-rt ^{0}C, 1h, 95%. (b) $CaCl_2$, HCl, 80-90 ^{0}C, 4h, 93%. (c) THF, K_2CO_3, 8h, piperazine, 87%. (d) 1-Bromoethanol, K_2CO_3, acetonitrile, 80-85 ^{0}C, 2h, 82%. (e) 1-Bromoacetic acid, K_2CO_3, acetonitrile, 80-85 ^{0}C, 5h, 80%.

Thus confirmed alcohol compound **6** was reacted with α-bromoacetic acid in presence of K_2CO_3 at acetonitrile reflux to yield the target molecule of cetirizine **1** in very good yields as shown in the scheme 2. In conclusion, we have developed a simple and efficient synthetic route for the preparation of racemic cetirizine in five steps with an overall yield in 50%. This route was applicable for large scale synthesis of cetirizine very conveniently. All the products were characterized by their ^{1}HNMR, IR and mass spectroscopy data.

Experimental section:

General: Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}HNMR spectra were recorded on Bruker-300 MHz, spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

[4-Chlorophenyl (phenyl)] Methanol (3): To a stirred solution of (4-chlorophenyl (phenyl) methanone, **2** (5 g, 23.1 mmol) in methanol (25 mL) was added sodium boro hydride (1.3 g, 34.6 mmol) in portions at 0 ^{0}C for a period of 15 min and continued stirring at room temperature for 1hour. The progress of the reaction was monitored by TLC. After completion of the starting material as indicated by TLC, the reaction mixture was quenched by adding crushed ice. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x25 mL). The combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel 60-120 mesh, and ethyl acetate-hexane as elutents in 2:8 ratio. The pure product was obtained as a white solid, yield 4.8 g (95%). MP. 55-56^{0}C. IR (KBr): υ 3360, 3062, 3030, 2899, 1594, 1486, 1452, 1401, 1340, 1282, 1188, 1086, 1015, 918, 846, 797, 761, 701, 620 cm.$^{-1}$; ^{1}HNMR ($CDCl_3$): δ 5.75 (d, 1H, *J* = 5.5 Hz), 7.20-7.35 (m, 9H).; EIMS *m/z* (%): 220 (m^{+1} 15), 201 (85), 182 (100), 167 (30), 102 (35), 65 (10).

1-Chloro-4-[chloro (phenyl) methyl] benzene (4): To a stirred solution of [4-chloro phenyl (phenyl)] methanol **3** (4.5 g, 20.6 mmol) in hydrochloric acid (20 mL) was added calcium chloride (3.2 g, 28.8 mmol) at room temperature. The resulting reaction mixture was refluxed for 4h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (2x25 mL). The combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was obtained as a light brown liquid, yield 4.5 g (93%). IR (neat): υ 3062, 3030, 2926, 2812, 1596, 1490, 1452, 1405, 1289, 1227, 1182, 1089, 1013, 846, 803, 756, 700, 603 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 6.02 (s, 1H), 7.25-7.38 (m, 9H).; EIMS *m/z* (%): 237 (m$^+$ 10), 203 (40), 201 (100), 166 (20) 124 (15), 109 (15), 91 (10), 71 (25), 56 (10).

1-[(4-chlorophenyl) (phenyl) methyl] piperazine (5): To a stirred solution of 1-chloro-4-[chloro (phenyl) methyl] benzene, **4** (4g, 16.9 mmol) in tetrahydrofuran (40 mL) was added potassium carbonate (4.3g, 33.7 mmol), piperazine (1.5g, 16.9 mmol) and a catalytic amount of phasetransfer catalyst (tetrabutyl ammonium iodide). The resulting reaction mixture was refluxed for 8h. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and the cake was washed with ethyl acetate (2x15 mL). The combined filtrate was concentrated under reduced pressure and the residue was acidified by adding HCl to P^H = 4. At this stage, the compound was washed with hexane (2x15 mL) and the compound again basified to P^H = 8 and extracted ethyl acetate (2x25 mL). The combined ethyl acetate layers was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was obtained as light yellow syrup, yield 4.2 g (87%). IR (neat): υ 3422, 2924, 2854, 1458, 1282, 1090, 1004, 804, 759, 703 cm.$^{-1}$; ^{1}H N MR ($CDCl_3$): δ 2.58 (brs, 4H), 3.08 (brs, 4H), 4.25 (s, 1H), 7.15-7.35 (m, 9H).; EI MS *m/z* (%): 289 (m^{+2} 30), 287 (m$^+$ 70), 203 (40), 201 (100), 87 (10).

2-[4-((4-Chlorophenyl)(phenyl)-methyl)-piperazin-1-yl]-Ethanol(6):To a stirred solution of 1-[(4-chlorophenyl)(phenyl)-methyl]-piperazine compound, **5** (0.6g, 2.1 m mol) in acetonitrile (10 mL) was added potassium carbonate (0.58 g, 4.2 mmol). After some time stirring was added bromoethanol (0.26g, 2.1 mmol) and the resulting reaction mixture was refluxed for 2 hours. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and residue was dissolved in water and extracted with ethyl acetate (2x15 mL). The combined organic layers was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was obtained as light yellow syrup, which was purified by column chromatography using silica gel (60-120 mesh) while eluting with ethyl acetate and hexane mixture in 4:6 ratio. The pure product was obtained in yield, 0.56 g (82%). IR (neat): υ 2929, 2858, 1459, 1375, 1280, 1095, 935 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 2.28-2.45 (m, 4H), 2.48-2.60 (m, 6H), 3.55 (t, 2H, *J* = 6.0 Hz), 4.19 (s, 1H), 7.12-7.38 (m, 9H).; EIMS *m/z* (%): 331 (m$^+$ 95), 315 (10), 287 (20), 201 (100), 129 (10), 89 (10).

2-[2-(4-((4-Chlorophenyl)(phenyl)-methyl)-piperazin-1-yl)-ethoxy]-Acetic acid (1): To a stirred solution of 2-[4-((4-Chlorophenyl)(phenyl)-methyl)-pipera zin-1-yl]-ethanol, compound, **6** (0.5g, 1.51 mmol) in acetonitrile (10 mL) was added potassium carbonate (0.41g, 3 mmol) and 1-bromoacetic acid (0.2g, 1.51 mmol). The resulting reaction mixture was refluxed for 5 hours. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and residue was dissolved in water and extracted with ethyl acetate (2x15 mL). The combined organic layers was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was obtained as light yellow syrup, which was purified by column chromatography using silica gel (60-120 mesh) while eluting with ethyl acetate and hexane mixture in 4:6 ratio. The pure product was obtained as a thick syrup, yield, 0.47 g (80%). ^{1}HNMR ($CDCl_3$): δ 2.20-2.30 (m, 2H), 2.55-2.72 (m, 4H), 3.05-3.25 (m, 4H), 3.60-3.80 (m, 4H), 4.20-4.30 (m, 1H), 7.15-7.36 (m, 9H).

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