Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(3):982-987

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of 3-hydroxy desloratadine, the hydroxyl metabolite of loratadine

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ABSTRACT

*The structure of a major active metabolite of the nonsedating antihistamine loratadine was confirmed by synthesis. The metabolite **3** was prepared from 3-methyl pyridine in twelve steps.*

Key words: Loratadine; Desloratadine; 3-Hydroxydesloratadine; Metabolite

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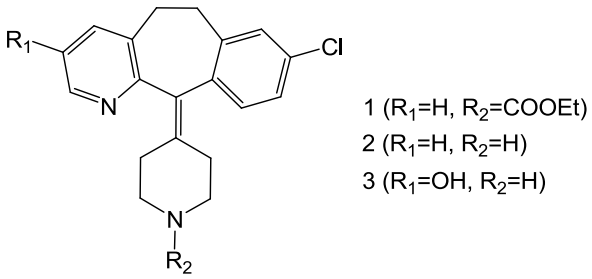
INTRODUCTION

Allergic rhinitis (AR) is an IgE-mediated disease that can impact the quality of life and work of affected individuals. Antihistamines were introduced more than 50 years ago for the treatment of AR [1-2]. They can be classified into three groups. First-generation antihistamines such as promethazine and ketotifen are clinically effective, but they have a considerably limited use by their sedative and anticholinergic effects. Second-generation antihistamines such as cetirizine, loratadine**1** and mizolastine have significantly fewer sedative and anticholinergic effects than first-generation [3]. New generation antihistamines include fexofenadine, levocetirizine, desloratadine**2** and rupatadine. While many of these agents were largely devoid of CNS (central nervous system) side effects, their tendency for drug-drug interactions (e.g., terfenadine and astemizole) resulted in an increase incidence of cardiotoxicity. Furthermore, some of the second-generation H_1 antagonists exhibited weak anti-inflammatory properties and had no effect on nasal congestion. These observations emphasized the need for newer anti-allergic agents with a potent and long lasting activity, low liability to enter into the brain and lacking cardiotoxic potential [4].

Loratadine**1** is a potent, long-acting H_1-antihistamine in clinical use [5-7]. Loratadine**1** undergoes extensive first pass metabolism to form the active metabolite desloratadine**2 [**8].Among the H_1 antagonists in clinic development, the third-generation H_1 antagonists desloratadine**2** is one of the most widely studied. Desloratadine**2** exhibits qualitatively similar pharmacodynamic activity with a relative oral potency in animals two to three-fold greater than loratadine probably due to a higher affinity for histamine H_1 human receptor [9]. Then desloratadine**2** was hydroxylated at several positions. Many studies showed 3-hydroxy desloratadine is a major active metabolite in these hydroxylated derivatives [10-13]. In order to confirm the structural assignments of this hydroxylated metabolite and also evaluate its pharmacological, we report herein the first synthesis of ol**3** in this context.



Scheme 1 Loratadine and its metabolites

EXPERIMENTAL SECTION

2.1 General methods

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ or CD3OD at ambient temperature with a Bruker DRX 300. Chemical shift (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak. Coupling constants, *J*, are reported in Hertz. Mass spectra were recorded using a Quattro micro API mass spectrometer. Chemical purities were determined by an Agilent 1200 HPLC with a XDB-C18 column, 5 μm, 4.6×150 mm. Thin layer chromatography was performed on precoated aluminum sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 5% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60(Merck, Art, 9385). All moisture-sensitive reactions were carried out under rigorous anhydrous conditions under a nitrogen atmosphere using oven-dried glassware. Solvents were dried and distilled prior to use and solids were dried over P_2O_5 under reduced pressure.

Synthesis of 5-methylpyridine-3-sulfonic acid (**5**)

To a stirred solution of 3-picoline (30 g, 322 mmol) in 50% fuming H_2SO_4 (120 g) at 0 ℃ was added $HgSO_4$ (0.82 g). The mixture was heated at 220-230 ℃ for 16 hours. The reaction mixture was cooled to 60 ℃ in the air and then cooled in ice bath and diluted with anhydrous ethanol (300 mL) and the resulting alcoholic solution was cooled to 0 ℃. After stirred at this temperature for 4 hours, the precipitate was came out and filtered to give **5** (41 g, 46%) as a brown solid. ^{1}H NMR (DMSO, 300 MHz): δ 8.53 (d, J=1.5 Hz, 1H), 8.72(d, J=1.5 Hz, 1H), 8.86 (d, J=1.5 Hz, 1H), 2.49(s, 3H).

Synthesis of 5-methylpyridine-3-ol (**6**)

The stainless steelreactor was loaded with NaOH (120 g, 3.0 mol) and heated about 180 ℃. Di-water (62 mL, 3.44 mol) and **5** (40g, 239 mmol) was added to the reaction. The reaction was heated to about 210 ℃ for 30 minutes. The reaction mixture was cooled at room temperature and diluted with water (800 mL). The aqueous phase was neutralized to pH 6 and extracted with CH_2Cl_2 (3×200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to afford **6** (16g, 61%) as a light yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07(d, J=1.5 Hz, 1H), 7.91(d, J=1.5 Hz, 1H), 7.21(d, J=1.5 Hz, 1H), 2.49(s, 3H).

Synthesis of 3-methoxy-5-methylpyridine (**7**)

To a solution of **6** (4.88 g, 44.72 mmol) in dry THF was added triphenyl phosphine (28g, 89.43 mmol), diethyldiazadicarboxylate (15.58 g, 15.56 ml, 89.43 mmol) and dry methanol (2.5 g, 80.49 mmol) below 20 ℃. After complete addition, the reaction was stirred at room temperature for 12hours. The reaction mixture was quenched with H_2O (10 mL). The solvent was removed under vacuum. The residue was dissolved in toluene (500 ml) and washed with 3MHCl (3×150 mL). The combined aqueous phases were cooled in ice bath and basified with 50% NaOH solution to pH 12 and extracted with ethyl acetate (3×150 ml). The combined organic phases were then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate (7:3; v/v) to afford **7**(3.19 g, 57%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13(d, J=1.5 Hz, 1H), 8.06(d, J=1.5 Hz, 1H), 7.01(d, J=1.5 Hz, 1H), 3.84(s, 3H), 2.32(s, 3H).

Synthesis of 3-methoxy-5-methylpyridine-N-oxide (**8**)

Toa solution of **7** (8.68 g, 70.48 mmol) in acetic acid (52.08 mL) was added 30% H_2O_2 (8.68 mL) and stirred at 120 ℃ for 12 hours. The reaction mixture was evaporated to dryness and co-evaporated with toluene to afford **8** (9.9 g, 98%) as a brown semi-solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 (d, J=1.5 Hz, 1H), 7.80(d, J=1.5 Hz, 1H), 6.74(d, J=1.5 Hz, 1H), 3.83(s, 3H), 2.29(s, 3H).

Synthesis of 2-cyano-5-methoxy-3-methylpyridine (**9a**)

To a solution of **8** (10 g, 71 mmol) in dry CH_2Cl_2 (100 mL) was added dimethylcarbamyl chloride (9.9 g, 8.48 mL, 92 mmol) and trimethylsilyl cyanide (9.14 g, 12.38 mL, 92 mmol). After addition, the reaction mixture was stirred at room temperature for 8 hours. It was cooled in ice bath, diluted with CH_2Cl_2 (100 mL) and washed with saturated K_2CO_3 solution (2×40 mL). The CH_2Cl_2phase were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 ×30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography using hexane/ethyl acetate (10:1; v/v) to afford **9a**(2.8 g, 30%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, J=1.5 Hz, 1H), 7.07(d, J=1.5 Hz, 1H), 3.91(s, 3H), 2.54(s, 3H).

Compound **9b** was isolated by column chromatography using hexane/ ethyl acetate (9:1; v/v) as a brown crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.12(d, 1H, J=1.5 Hz), 7.14(d, 1H, J=1.5 Hz), 3.95(s, 3H), 2.43 (s, 3H).

Synthesis of 2-[(tert-butylamino)carbonyl]-5-methoxy-3-methylpyridine (**10**)
A suspension of **9a** (1.2 g, 8 mmol) in dry tert-butyl alcohol (2.4 mL) was heated at 45 ℃. Concentrated sulfuric acid (1.2 mL) was added over 45 minutes. The mixture was heated to 60 ℃ and maintained for 40 minutes. The reaction mixture was cooled in ice bath, then diluted with toluene (40 mL) and water (20 mL), basified with concentrated aqueous ammonia to pH 11. The organic phase was separated and the aqueous layer was extracted with toluene (4×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate (8:2; v/v) to afford **10**(1.56 g, 87%) as light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06(d, 1H, J=1.5 Hz), 7.95(brs, 1H), 7.02(d, 1H, J=1.5 Hz), 3.88(s, 3H), 2.73(s, 3H), 1.47(s, 9H).

Synthesis of 3-[2-(3-chlorophen)ethyl]-5-methoxy-N-(tert-butyl)-2- pyridinecarboxamide(**11**)
To a cold (-60 ℃) solutionof **10** (2.01 g, 8.77 mmol) in dry THF (20 mL) was added n-butyllithium in hexanes solution (1.6 N, 12 mL)in 25 minutes while the temperature was maintained at -60 ℃. The solution turned deep red after 1 equiv n-butyllithium was added. Sodium bromide (0.09 g) was added and the mixture stirred for 10 minutes. A solution of chlorobenzyl chloride (1.41 g, 1.1 ml, 9 mmol) in THF (4 mL) was added in 35 minutes while the temperature was maintained at -60 ℃. After addition, the solution became dilute and red color became faint. The reaction mixture reaction was stirred for 45 minutes. Water (20 mL) was carefully added until the red color disappeared. The mixture was diluted with ethyl acetate (80 mL) and separated. The aqueous layer was further extracted with ethyl acetate (2× 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ ethyl acetate (9:1; v/v) to afford **11**(2.46 g, 82%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300MHz): 8.04(d, J=1.5 Hz, 1H), 7.86(brs, 1H), 7.21(d, J=1.5 Hz, 1H), 6.8-7.2(m, 4H), 3.84(s, 3H), 3.47(t, J=9 Hz, 2H), 2.96(t, J=9 Hz, 2H), 1.48(s, 9H).

Synthesis of 3-[2-(3-chlorophenyl)ethyl)]-5-methoxy-2-pyridinecarbonitrile (**12**)
Asolution of **11** (1.6 g, 4.61mmol) in phosphorus oxychloride(5.9 mL, 46.13 mmol) was heated at 115 ℃ for 3 hour. Excess phosphorus oxychloride was removed under reduced pressure and the resulting solution was diluted with ice-water(20 mL) and CH_2Cl_2(30 mL). The solution was adjusted by saturated Na_2CO_3 solution to pH 10 while the temperature was maintained at 25-30 ℃. The CH_2Cl_2 phase was separated and aqueous phase was extracted with CH_2Cl_2. The combined organic layers was washed with saturated Na_2CO_3 solution and dried over Na_2SO_4. The volatiles were removed under reduced pressure to afford **12** (1.2, 96%) as a brown solid.^{1}H NMR ($CDCl_3$, 300 MHz): 8.24(d, J=1.5 Hz, 1H), 7.21(d, J=1.5 Hz, 1H), 6.8-7.1(m, 4H), 3.84(s, 3H), 3.09-3.29(m, 2H), 2.94-3.05(m, 2H).

Synthesis of (1-Methyl-4-piperidinyl)[(3-[2-(3-chlorophenyl)ethyl]-5-methoxy-2- pyridinyl)methanone(**13**)
To a solution of compound **12** (1.5 g, 5.52 mmol) in dry THF(20 mL) was added of (N-methylpiperidyl) magnesium chloride(1.1 N, 6 mL) in dry THF over 1 h while the temperature was maintained at 40-45 ℃. The reaction mixture was maintained at 45 ℃ for an additional 1 hour. The reaction mixture was cooled to 0 ℃ and quenched by the addition of 2N hydrochloric acid to below pH 2 and the resulting solution was stirred at room temperature for 15 minutes. The excess THF was removed under reduce pressure and the resulting solution was cooled in ice bath. The solution was basified by the addition of saturated Na_2CO_3 solution to pH 8. The solution was extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate/MeOH (8:2:1; v/v/v) to afford **13**(1.98 g, 97%) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.20(d, J=1.5 Hz, 1H), 7.18(m, 3H), 7.08(d, J=1.5 Hz, 1H), 6.83(d, J=1.5 Hz, 1H), 3.83(s, 3H), 3.17(m, 2H), 2.85-2.95(m, 4H), 2.30(s, 3H), 2.10(m, 2H), 1.66-1.83(m, 4H).

Synthesis of 8-Chloro-6,11-dihydro-3-methoxy-11-(1-methyl-4-piperdylidene)-5H- benzo[5, 6] cyclohepta [1, 2-b]pyridine(**14**)

A solution of **13** (1.98 g, 6.32 mmol) in trifluoromethane sulfonic acid (10 g, 6.9 ml, 106.48 mmol) was heated at 75 ℃ for 12 hours. The reaction mixture was quenched with ice water (10ml) and adjusted to pH 10 with saturated Na_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3×40 ml) and the combined organic phases were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate /MeOH/NH_4OH (9: 1: 0.05; v/v/v) to afford **14** (1.01 g, 60%) as a purple solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.11(d, J=1.5 Hz, 1H), 7.12-7.18(m, 3H), 6.94(d, J=1.5 Hz, 1H), 3.81(s, 3H), 3.29-3.47(m, 2H), 2.68-2.85(m, 4H), 2.29(s, 3H), 2.24-2.61(m, 6H).

Synthesis of 8-Chloro-6,11-dihydro-3-methoxy-11-(1-methyl-4-piperdylidene)-5H- benzo[5, 6]cyclohepta [1, 2-b]pyridine (**15**)

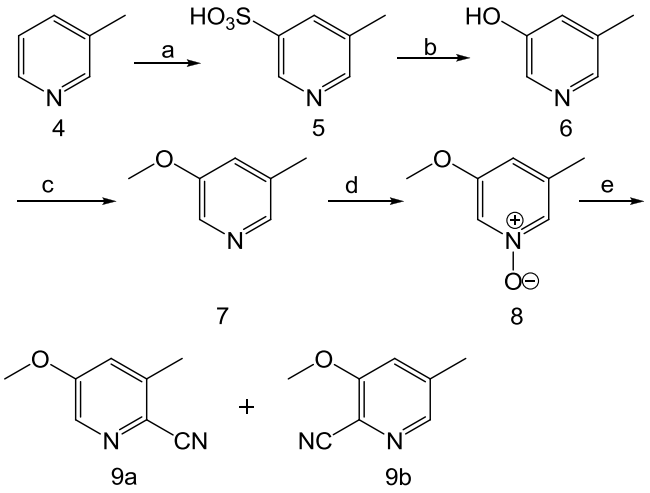
To a solution of **14** (0.41 g, 1.1 mmol) in dry CH_2Cl_2 (3 mL) was added 1-chloroethyl chloroformate. The reaction mixture was heated at 40 ℃ for 1 hour. The bulk of the CH_2Cl_2 and 1-chloroethyl chloroformate was removed by distillation. The residue was quickly flushed by the column chromatography, eluted with (ethyl acetate) to give brown solid (0.14 g). The solid was dissolved in methanol (5 mL) and stirred at room temperature for 8 hours. Solvent was removed to afford **15** (0.12 g, 30%) as a brown solid. The column was flushed by the eluent using MeOH/MeOH saturated with gaseous ammonia (95:5; v/v) to give the starting material **14** (0.35g, 60%). ^{1}H NMR ($CDCl_3$, 300 MHz): 8.09(d, J=1.5 Hz, 1H), 7.11-7.16(m, 3H), 6.94(d, J=1.5 Hz, 1H), 3.81(s, 3H), 3.40(m, 2H), 3.12(m, 2H), 2.70-2.87(m, 4H), 2.34-2.48(m, 4H).

Synthesis of 3-hydroxy desloratadine(**3**)

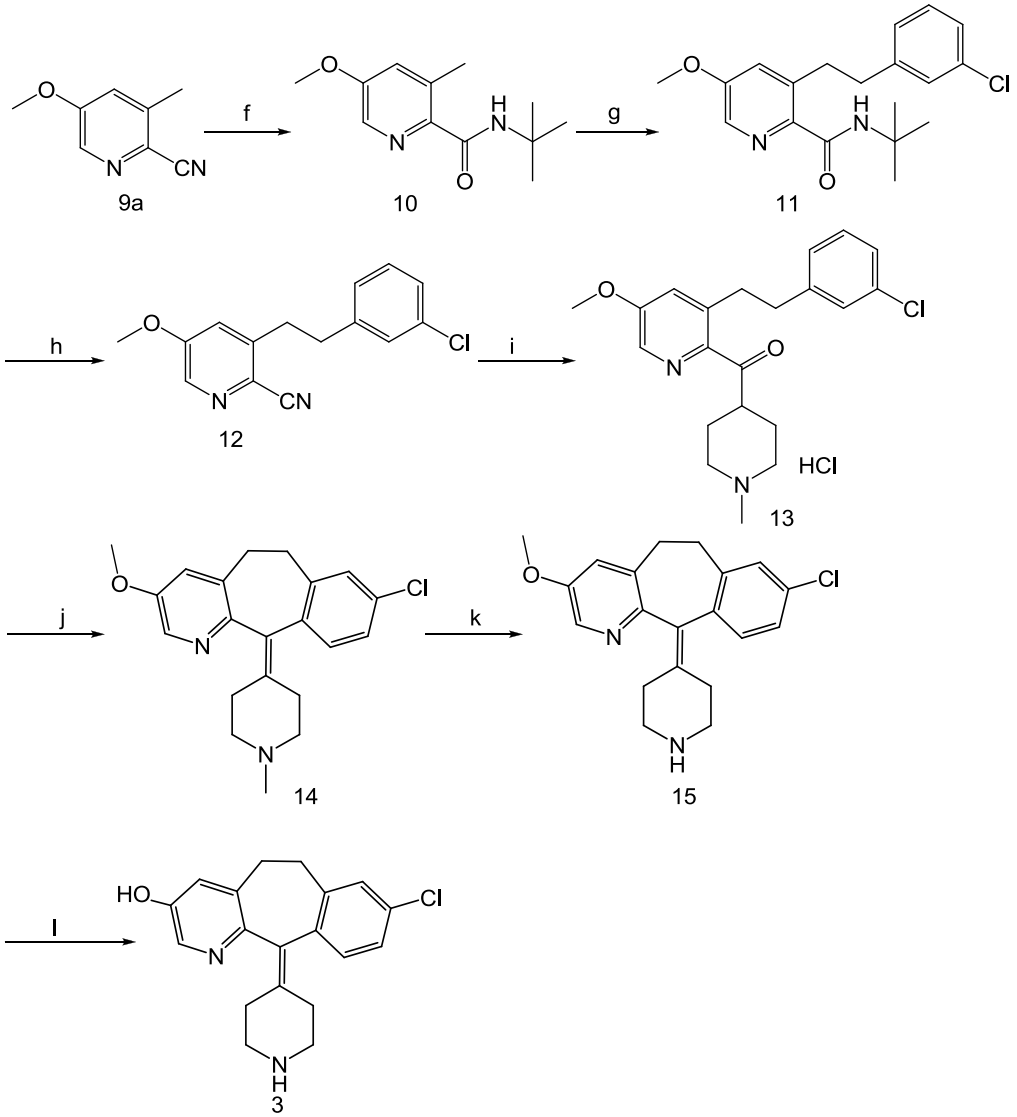
To a solution of **15** (0.3 g, 0.88 mmol) in dry CH_2Cl_2 (5 mL) was added BBr_3 (3.3 g, 13.2 mmol) in CH_2Cl_2 (2 mL) at -20 ℃. After addition, the reaction was stirred at room temperature for 12 hours. The reaction mixture was cooled in ice/salt bath, quenched with concentrated aqueous ammonia to pH 6. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$/MeOH(9:1; v/v) (4×5 ml). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography CH_2Cl_2 /MeOH/MeOH saturated with gaseous ammonia (8:1:1; v/v/v) to afford **3**(0.2 g, 69%) as a light yellow solid. ^{1}H NMR(CD_3OD, 300 MHz): 7.88(d, J=1.5 Hz, 1H), 7.08-7.24(m, 3H), 7.03(d, J=1.5 Hz, 1H), 3.30-3.42(m, 2H), 3.30(brs, 1H), 3.06-3.17(m, 2H), 2.75-2.86(m, 4H), 2.28-2.51(m, 4H). ESI-MS(m/z) 326$(M+1)^+$, 328$(M+3)^+$. HPLC (XDB-C18, CH_3OH/10mmol/L NaH_2PO_4= 55/45, 1.0 mL/min): t_R 6.05 min (>98.1%).

RESULTS AND DISCUSSION

While compound **3** is also commercially available in milligram quantities, its synthesis has not been described in the literature. Initially we want to prepare 3-hydroxydesloratadine**3** from desloratadine**2**, but unfortunately without success. It is hard to introduce hydroxyl group to pyridine ring, the reaction was so complex and we haven't been obtained the target product. Our strategy then turned to modify pyridine ring from 3-methyl pyridine **4** (Scheme 1). 3-Picoline**4** was first converted to sulfonic derivative **5** with fuming H_2SO_4 and $HgSO_4$ at 220 ℃ for16 hours in 46% yield. The product was easily recrystallized from ethanol.[14] Treatment of compound **5** with NaOH and water at 210℃ produced 5-hydroxy-3-picoline **6** in 61% yield. Direct protection of the hydroxyl group in compound **6** with CH_3I give low yield due to N-methyl pyridine salt formed. Compound**6** could be protected via mitsunobu reaction.[15]Such protection proved effective, and **7** was formed with57% yield in presence of triphenyl phosphorous, diethyl azodicarboxylate and methanol.Direct oxidation of compound **7**with 30% H_2O_2 solution in acetic acid affordedcompound **8** in 97% yield. Treatment ofcompoud**8** with dimethylcarbamyl chloride and trimethylsilyl cyanide in dichloromethane afforded a 1/2 mixture of the isomeric nitriles **9a**and **9b** in 90% yield[16]. The nitriles[R_f=0.55(major), R_f=0.5(minor); 30% EtOAc in hexanes] were separated and identified as 6-cyanide ether **9a** (minor) and the corresponding 2-cyanide ether **9b**(major). These assignments were made on the basis of their NMR spectra. The C-2 in pyridine proton resonance of the minor **9a** was at 8.12 ppm while the C-6 in pyridine proton resonance of the major **9b** was at 8.21 ppm. Compound **9a** was a methoxy derivative of the starting material for synthesis of loratadine. The subsequent procedures were similar with the synthesis procedures of loratadine(Scheme 2).[17]Nitrile**9a**was protected as the tert-butylamide**10** through treated with tert-butyl alcohol and sulfuric acid via a Ritter reaction in 87% yield[18].The dianion of this amide was readily formed with n-butyllithium at -40 ℃, and then was alkylated with m-chlorobenzyl chloride to give the (chlorophenethyl)pyridine**11**in 82% yield. The amide **11**was converted to nitrile **12**with phosphorus oxychloride in 96% yield without special treatment. The nitrile **12** was alkyated with (N-methylpiperidyl) magnesium chloride to give the imine intermedia, which was hydrolyzed with 2Mhydrochloric acid solution to give ketone hydrochloride **13** with 97% yield. The cyclodehydration of ketone**14**intrifluoromethane sulfonic acid formed loratadine derivative **15** with 60% yield. Compound **15** was treated with **3**equiv of 1-Chloroethyl chloroformate in CH_2Cl_2 at 40 ℃, then stirred with MeOH to give 3-methoxy deslotadine**16** in 30% yield and recovery starting material**15** in 60% yield. Deprotection of **16**with BBr_3 in CH_2Cl_2 produced 3-hydroxydesloratadine**3** with 83% yield. The structure of **3** was confirmed by NMR and MS experiments.



Scheme 1.Synthesis of 5-methoxy-3-methylpicolinonitrile. Reagents and conditions:(a) fuming H_2SO_4, $HgSO_4$, 220 ℃; (b)NaOH, H_2O, 210 ℃; (c) PhP_3, DEAD, MeOH, THF, rt; (d) 30%H_2O_2, 115 ℃; (e)$(CH_3)_2NCOCl$, $(CH_3)_3SiCN$, CH_2Cl_2, rt;



Scheme 2. Reagents and conditions:(f)H_2SO_4, t-BuOH; 45 ℃; (g)n-BuLi, m-chlorobenzyl chloride, THF, -60 ℃; (h)$POCl_3$, 115 ℃; (i)(i)(N-methylpiperidyl) magnesium chloride, THF; (ii)aqueous HCl; (j)CF_3SO_3H, 75 ℃; (k)(i)Chloroethylchloroformate, CH_2Cl_2, 40 ℃; (ii)MeOH; (l)BBr_3, CH_2Cl_2, 0 ℃.

CONCLUSION

We have designed an efficient process for the synthesis of 3-hydroxy desloratadine**3** and this process is being used on a multikilo scale for subsequent analog work in pharmacokinetic and efficacy studies. The key intermediate**9a** was also convenience synthesized in five steps.

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