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Transfer Hydrogenolysis: An Improved Synthesis of (*R*)-(-)-α-Methyl Histamine

Richard J. Friary, Pietro Mangiaracina,* Mehdi Nafissi, Steven C. Orlando, Stanley Rosenhouse, Vera A. Seidl, and Neng-Yang Shih

Schering-Plough Research Institute
2015 Galloping Hill Road, Kenilworth, N. J. 07033-0539

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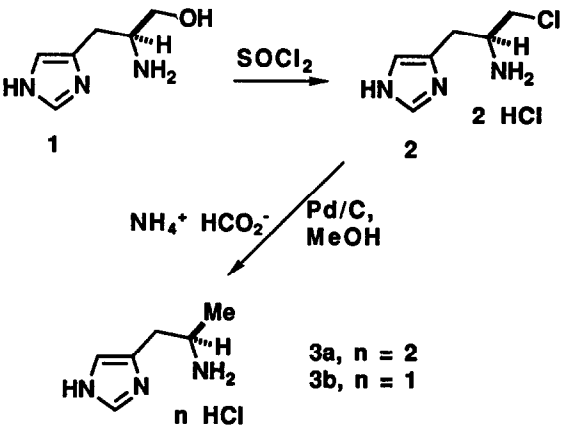
Abstract: *Ammonium formate in the presence of palladium on carbon in methanol reacted with (S)-(+)4-(2-Amino-3-chloro-propyl)-imidazole to give optically pure (R)-(-)-α-methyl histamine at atmospheric pressure.*

Optically pure (*R*)-(-)-α-methyl histamine (3) selectively agonizes the histamine H_3-receptor,[1a] a finding which renewed interest in the pharmacology and synthesis of this compound.[1b] Not commercially available until recently, (*R*)-α-methyl histamine remains expensive[2] and can be difficult to prepare. Indeed, attempts to repeat the last step of a brief, published[3] synthesis afforded none of **3a**. Pushed and pulled by a need for **3a** and a failure to make it, we improved the synthesis and report our results here. They comprise atmospheric-pressure transfer hydrogenolysis of alkyl chloride **2** as well as more vigorous conditions for carrying out high-pressure hydrogenolysis of **2** than those originally reported.



One published synthesis calls for conversion of L-histidinol **1** to the chloromethyl derivative **2**, an uneventful step in our hands, and for catalytic reduction of **2** to **3a**.[3] Our initial difficulty in making **3a** lay in reducing **2**. This reaction reportedly occurs under 25 atm of hydrogen in the presence of 10% Pd-on-C and sodium acetate in acetic acid containing 10 vol-% of water at room temperature.[3] Yet, none of **3a** resulted when we treated compound **2** according to the published procedure.

Compound **3a** formed in good yield (86%) under more vigorous conditions than those reported. To attain this result, we ultimately increased the pressure by half, doubled the time and solvent volume, and tripled the amounts of catalyst and sodium acetate. Chloromethyl derivative **2** was then completely changed to **3a**, which was isolated by crystallization. Merely increasing the pressure from 25 to 34 atm was insufficient, however. Although it did give **3a**, the yield amounted only to 30%.

Another reported reduction, this one of the racemic bromomethyl derivative corresponding to **2**, succeeded directly, providing α-methyl histamine as the dihydrobromide salt.[4] In this case, the published procedure was still somewhat unsatisfactory, because it called for a heated Paar bomb. Such vessels are available only in a limited number of sizes, and this restriction decreases the reduction scale.

We found that high-pressure hydrogenolysis of chloromethyl derivative **2** was unnecessary. Reduction of optically active **2** took place at atmospheric pressure, simply by means of catalytic transfer hydrogenolysis.[5] The monohydrochloride **3b** formed in 2–3 hrs on refluxing dihydrochloride **2** with 10% Pd-on-C in methanol containing ammonium formate. Chemical yields of **3b** consistently exceeded 90%, and the reaction occurred on a scale as large as 100 grams of **2**. For comparison, we converted the monohydrochloride **3b** to dihydrochloride **3a**, and also converted a sample of **3b** to amide **4**. Unsurprisingly, this sample of **4** was optically pure.

The resulting sample of α-methyl histamine **3a** contained an excess of the *R*-enantiomer, as expected. The enantiomeric excess (ee) surpassed or equalled 99%. Fluorine NMR spectroscopy provided this value for the optical purity of the diastereomeric Mosher amide **4**, made from **3** and (*S*)-(+)–α–methoxy-α-(trifluoromethyl)phenylacetyl chloride.[6] The overall chemical conversion to crude amide **4** amounted to 94%. Amidation of **3** with 2 equivalents of the acid chloride followed by selective hydrolysis of the resulting diamide **5** yielded monoamide **4**.

4, R = H
5, R = COC(Ph)(OMe)CF_3

For validation, we made samples of the corresponding amides from racemic α-methyl histamine and from an artificial 99:1 mixture of *R* and *S* enantiomers. Baseline resolution of the trifluoromethyl and methyl group resonances was apparent in ^{19}F and ^{1}H NMR spectra of these diastereomeric amide mixtures. Integration of the ^{19}F NMR spectra furnished the ee-values.

In summary, atmospheric-pressure hydrogenolysis of **2** made **3a** more accessible than did high-pressure hydrogenolysis. For safety, high-pressure experiments require special laboratories equipped with blow-out walls, a need averted by hydrogenolysis at ordinary pressure.

As far as we know,[7] the (expected) conversion of **2** to **3b** constituted the first example of transfer hydrogenolysis of an alkyl chloride.

EXPERIMENTAL SECTION[8]

(S)-(+)4-(2-Amino-3-chloropropyl)-imidazole (2)—Prepared from a commercial sample (Aldrich Chemical Co.) of (*R*)-(-)-4-(2-amino-3-hydroxypropyl)-imidazole (**1**) according to ref 3, compound **2**, mp 199–201° (d.) (from ethanol) (lit.[3] mp 196°), $[\alpha]_D^{26}$ = +17.6° (*c* = 1.04, water) (lit.[3] $[\alpha]_{589}^{20}$ = +13.4° (*c* = 0.001 [*sic*], water)) was obtained in a yield of 58%; ^{13}C NMR (DMSO-d_6): 134 (*C* -2), 127 (*C* -4), 118 (*C* -5), 50 (CH_2Cl), 44 (*C* HNH_2), 25 (*C* H_2); MS: 160 (2, M^+), 110 (14), 82 (90), 81 (86), 80 (12), 78 (38), 55 (18), 54 (21), 44 (6), 43 (15), 42 (19).

(R)-(-)4-(2-Aminopropyl)-imidazole dihydrochloride (3a). From High-Pressure Hydrogenolysis—A mixture of **2** (7.50 g, 32.2 mmol), water (450 mL), acetic acid (50 mL), sodium acetate (14.7 g, 179 mmol), and 10% palladium on carbon (10 g) was kept in an autoclave at 25° C under 500 psi of hydrogen for 144 hrs. The catalyst was removed by filtration, and the *p*H of the filtrate adjusted to 1 with concentrated hydrochloric acid. Solvents were evaporated and the residue dissolved in ethanol. Precipitated salts were

removed by filtration and washed with ethanol. Combined filtrates, diluted with a little benzene, were evaporated. The residue was crystallized from a mixture of ethanol and acetone containing a little dichloromethane to give **3a** (6.15 g, 96%), pure according to tlc. Two recrystallizations from 2-propanol containing a little acetone provided **3a** (5.53 g, 86%), m.p. 165–167° (lit.[3] mp 176°), $[\alpha]_D^{29}$ = -3.7° (*c* = 1.03, water) (lit.[3] $[\alpha]_{589}^{20}$ = -5.1° (*c* = 0.01 [*sic*], water)); ^{1}H NMR (300 MHz, DMSO-d_6): 14.3, (br s, 1 H, ex., *H* -1and H-3), 9.10 (s, 1 H, *H* -2), 8.45 (br s, 3 H, ex., -NH_3^+), 7.55 (s, 1 H, *H* -5), 3.62 (br s, 1 H, C*H* (Me)NH_3^+), 3.12 (dd, 1 H, *J* (A–B) = 15, *J* (A–CH) = 6.3, CH_AH$_B$), 2.96 (dd, 1 H, *J* (A–B) = 15, *J* (B–CH) = 7.5, CH$_A$*H*$_B$), 1.22 (d, 3 H, J (C*H*$_3$-C*H*) = 6.4, C*H*$_3$); ^{13}C NMR (DMSO-d_6): 133.8 (*C* -2), 128.0 (*C* -4), 117.2 (*C* -5), 45.7 (CHNH$_2$), 28.7 (*C* H$_2$), 18.4 (*C* H$_3$); MS: 126 (3, [M + 1]$^+$), 125 (2, M$^+$), 82 (89), 81 (77), 44 (100).

For analysis, a sample was crystallized from 2-propanol with the aid of a Soxhlet extractor and had mp 175–176° and $[\alpha]_D^{27}$ = -3.8° (*c* = 1.02, water).

Anal. Calcd. for $C_6H_{13}Cl_2N_3$: C, 36.38; H, 6.61; Cl, 35.79; N 20.85. Found: C, 36.04; H, 6.48; Cl, 36.05; N, 20.85.

(R)-(-)4-(2-Aminopropyl)-imidazole monohydrochloride (3b). From Catalytic Transfer Hydrogenolysis—To a stirred solution of **2** (9.6 g, 41 mmol) in dry methanol (240 mL)under nitrogen were added 10% Pd-on-C (12.0 g) and anhydrous ammonium formate (20.5 g, 325 mmol). The resulting mixture was refluxed under nitrogen for three hrs. The cooled mixture was filtered through diatomaceous earth, and the mixture of filter aid and catalyst was washed with methanol (200 mL), dichloromethane-methanol (1:1 by vol, 200 mL), and dichloromethane (800 mL). The combined filtrates deposited a precipitate which was removed by filtration, washed with dichloromethane, and discarded. Combined filtrates again gave a precipitate which was similarly removed, washed, and discarded. When no more precipitate formed on dilution of the combined filtrates with dichloromethane, solvents were evaporated to give crude **3b** (6.2 g), as a foam; ^{1}H NMR (200 MHz, DMSO-d_6): 7.70 (s, 1 H, *H* -2), 7.0 (s, 1 H, *H* -4), 3.41 (sextet, 1 H, C*H*(Me)NH_3^+), 2.87 (dd, 1 H, J_{A-B} = 14.5, J_{A-CH} = 5.6, CH_AH$_B$), 2.70 (dd, 1 H, J_{A-B} = 14.5, J_{B-CH} = 8.0, CH$_A$*H*$_B$), 1.16 (d, 3 H, *J* = 6.3, C*H*$_3$); ^{13}C NMR: 17.3 (*C*H$_3$), 30.8 (*C*H$_2$), 46.4 (*C*HNH$_3^+$), 115.6 (*C* -5), 132.5 (*C*-4), 132.4 (*C*-2); MS (FAB): 126 (100, [M + 1]$^+$).

Analytically pure **3a** was obtained from crude **3b** as follows: an aqueous solution of crude **3b** (6.2 g) was passed through a column of Amberlite® IRA-400 (OH) (120 g) packed in water. Removal of the solvent from the effluent under reduced pressure gave the free base (3.87 g), which was dissolved in absolute ethanol (50 mL) and was cooled in an ice bath. Saturated ethanolic hydrochloric acid (70 mL) was added, after which the solvent was removed to give crude **3a** (6.0 g), which was recrystallized from a mixture of 2-propanol and acetone to give dihydrochloride **3a** (5.37 g, 66%), m.p.174–176°.

N-[2-(1H-imidazol-4-yl)-1(R)-methylethyl]-(S)–α–methoxy–α–(trifluoromethyl)benzeneacetamide (4)—To a mixture of *R*-(-)–α–methyl histamine dihydrochloride **3a** (25 mg, 0.126 mmol) in anhydrous N,N-dimethylformamide (0.5 mL) was added anhydrous triethylamine (88 mL, 0.63 mmol) and (*S*)-(+)–α–methoxy-α-(trifluoromethyl)phenylacetyl chloride (59 µL, 0.315 mmol). The resulting mixture was stirred for 17 hrs at 25° under nitrogen. The solution was concentrated and the residue, dissolved in water, was extracted with ethyl acetate. Combined extracts were dried and concentrated to give crude diamide **5**, all of which was used directly in the next step.

The sample of **5** was dissolved in methanol (4 mL) and a solution of anhydrous potassium carbonate (0.18 g, 1.3 mmol) in water (1.5 mL) was added. The resulting solution was then stirred 2 hrs at 25° under nitrogen and was concentrated. The residue, dissolved in water, was extracted with diethyl ether. Combined extracts were dried and concentrated to give monoamide **4**; ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (m, 6 H, C_6H_5 and *H* -2), 6.77 (s, 1 H, *H* -5), 5.0 (br s, 1 H, N*H*), 4.28 (m, 1 H, C*H*Me), 3.28 (s, 3 H, OC*H*$_3$), 2.83 (dd, 1 H, J_{A-B} = 14.8, J_{A-CH} = 5.7, CH_ACH$_B$), 2.74 (dd, 1 H, J_{A-B} = 14.8, J_{B-CH} = 6.6, CH_BCH$_A$), 1.14 (d, 3 H, *J* = 6.6, C*H*$_3$); ^{13}C-NMR: 165.5 (*C*ONH), 134 4 (*C* -2), 133.5, 132.2, 129.0, 128.0, 127.1, 123.4 (q, *J* = 290, *C*F$_3$), 116.7 (*C* -5), 83.4 (q, *J* = 26, *C*CF$_3$), 54.4 (OCH$_3$), 45.1 (*C* -7), 32.7 (*C*-6), 19.4 (CHCH$_3$); ^{19}F-NMR (400 MHz, $CDCl_3$): 7.24 ppm (s, C*F*$_3$); MS: 342 (100, [M + 1]$^+$), 341 (1, M$^+$).

Racemic N-[2-(1H-imidazol-4-yl)-1(R)-methylethyl]-(S)-α-methoxy-α-(trifluoromethyl)benzeneacetamide — Prepared from racemic α-methyl histamine and (*S*)-(+)–α–methoxy-a-(trifluoromethyl)phenylacetyl chloride as described above for **4**, this mixture showed the following, selected resonances. ^{1}H NMR (400 MHz, $CDCl_3$): 6.77 (s, 1 H, *H* -5), 6.69 (s, 1 H, *H* -5), 1.21 (d, 3 H, *J* = 6.6, C*H*$_3$), and 1.14 (d, 3 H, *J* = 6.6, C*H*$_3$); ^{19}F-NMR (400 MHz, $CDCl_3$): 7.24 (s, 3 F, C*F*$_3$) and 7.03 (s, 3 F, C*F*$_3$).

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8. General methods: uncorrected melting points were measured on a Thomas-Hoover Capillary Melting Point apparatus or on a MEL-TEMP apparatus. Optical rotations were measured with an Autopol™ III automatic polarimeter. NMR spectra were recorded on Varian 400 MHz and XL-300 instruments; ^{1}H, ^{19}F, and ^{13}C chemical shifts were determined in DMSO-d_6 solutions unless otherwise specified; proton-decoupled ^{13}C and ^{1}H δ-values are in parts per million downfield from tetramethylsilane. Assignments of ^{13}C resonances were made by means of DEPT experiments.[9] Coupling constants are in Hz. ^{19}F resonances are given in ppm downfield from external trifluoromethylacetic acid. Electron-impact mass spectra are reported unless specified otherwise; they were obtained with a Varian MAT 312 spectrometer. Parenthetical numbers immediately following *m/z*-values are relative ion intensities in per cent. Analtech provided silica gel F-254 tlc plates; developed plates were visualized by spraying with conc sulfuric acid-methanol (1:1 by volume), followed by charring. Organic solutions were routinely dried with magnesium or sodium sulfate after aqueous work-ups. Dry solvents purchased from the Aldrich Chemical Co. were used as supplied.

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