SHORT PAPER

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The selective synthesis of 1-methyl-1H-histamines†

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The selective synthesis of 1-methyl-1H-4-histamine (**1**) and 1-methyl-1H-5-histamine (**2**) via 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine (**3**) from commercially available histamine hydrochloride salt is described.

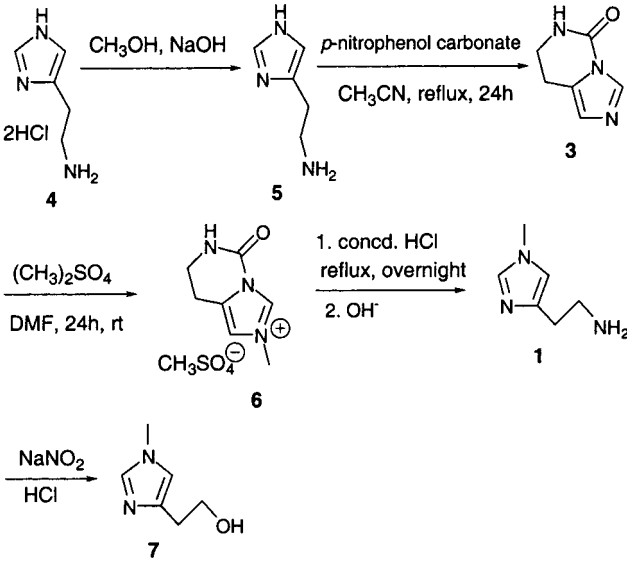
Keywords: 1-methyl-1H-histamines

The imidazole moiety of histidine is a common motif in biological systems.[1] For example, the active site of cytochrome *c* oxidase, the terminal membrane enzyme in the respiratory chain of mitochondria and aerobic bacteria, consists of a five-coordinate heme a_3 with an axial imidazole from a histidine residue and a copper atom (Cu_B) coordinated to three imidazole moieties.[2] In the course of our long-term project on designing and synthesising new active-site models of cytochrome *c* oxidase,[3] we became interested in employing 1-methyl-1H-4-histamine (**1**) and its isomer 1-methyl-1H-5-histamine (**2**) as pendant ligands on the distal face of the porphyrin ring. In this paper we present a modified procedure for selectively synthesising 1-methyl-1H-4-histamine (**1**)[4a,b, 4d–f] and a new synthetic approach to 1-methyl-1H-5-histamine (**2**)[4b,c] from 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin (**3**). The use of 1-methyl-1H-histamines allows us to connect these ligands to customised porphyrins via urea type links.[5]

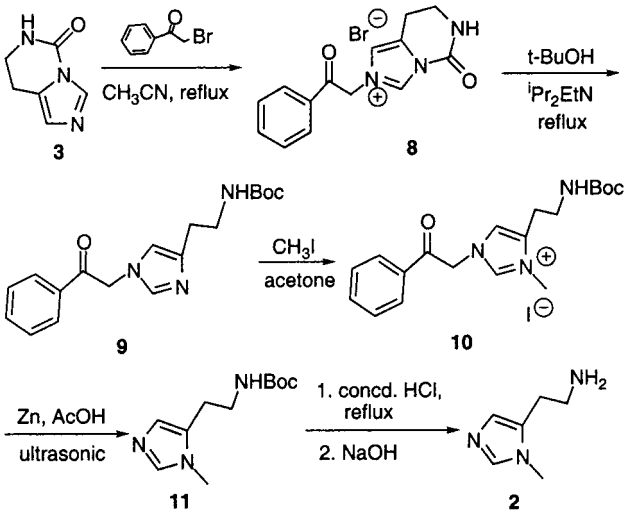
The synthesis of 1-methyl-1H-4-histamine (**1**) is accomplished with some modifications of the Durant's procedure.[4b] As shown in Scheme 1, histamine free base is obtained by treating commercially available histamine hydrochloride salt with NaOH in CH_3OH. The cyclization reaction of the free base with *p*-methoxyphenol carbonate[6] in CH_3CN gives 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine (**3**) in 74% yield. Compound **3** reacts with $(CH_3)_2SO_4$ to yield the quaternary salt **6**, which undergoes hydrolysis in acidic media forming 1-methyl-1H-4-histamine (**1**) in 74% yield. The procedure described herein is practical on a large-scale. Moreover, compound **1** can be converted to 4-hydroxyethyl-1-methyl-1H-imidazole (**7**) in 35% yield via diazotisation.[4e]

Several selective syntheses of 1-methyl-1H-5-histamine (**2**) from 1-methyl-1H-5-imidazole methyl carboxylate[4a] or N^{α}-phthaloylhistamine[4b,c] have been reported; we find that compound **2** can also be selectively prepared using 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine (**3**) as a precursor. As shown in Scheme 2, compound **3** reacts with 2-bromoacetophenone[7] to generate the quaternary salt **8**, which is treated with *t*-BuOH in the presence of $^{i}Pr_2EtN$ to give compound **9** in 46% yield. Compound **9** reacts with iodomethane to form the quaternary salt **10** in quantitative yield. The phenacyl group on the imidazole ring of compound **10** is readily removed in the presence of zinc powder in AcOH in an ultrasonic bath to form compound **11**. The subsequent hydrolysis of compound **11** in conc. HCl generates 1-methyl-1H-5-histamine (**2**) in 50% yield.

Furthermore, 1-methyl-1H-histamines can be introduced onto a porphyrin ring via a urea type linkage. For instance, *meso*-5,10,15,20-tetra(2′-aminophenyl)porphyrin (**12**) reacts with triphosgene in CH_2Cl_2 to yield an active isocyanate intermediate, which reacts further with 1-methyl-1H-4-histamine



Scheme 1



Scheme 2

(**1**) to generate the superstructure **13** in 61% yield (Scheme 3). Thus, we believe that 1-methyl-1H-histamine-based tripodal ligands[4f] that bind copper ion more tightly than single imidazole might also be attached on a porphyrin template via the same type of linkage.

In summary, we have described a modified procedure for selectively preparing 1-methyl-1H-4-histamine (**1**) and a new approach to 1-methyl-1H-5-histamine (**2**) via a common inter-

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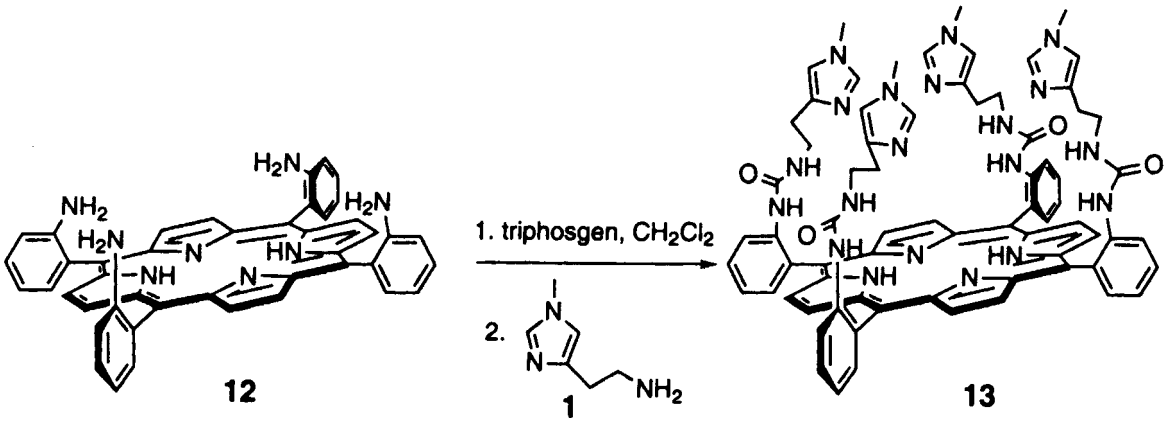

Scheme 3

mediate, 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine (**3**). 1-Methyl-1H-histamine-based multidentate ligand syntheses and their application in model studies of cytochrome *c* oxidase are currently under investigation and will be reported in due course.

Experimental

All melting points were recorded on a MEL-TEMP apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Infinity 60AR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian XL-400 spectrometer. Mass spectra were performed by the mass spectrometry facility at the University of California, San Francisco.

5-Oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine **(3)**: A mixture of histamine hydrochloride salt (10.0 g, 54.3 mmol) and NaOH (4.5 g, 109 mmol) in CH_3OH (400 ml) was refluxed for 2 h. The solvent was removed and the residue was refluxed with benzene (500 ml) overnight using a Dean-Stark equipment to remove traces of methanol and water formed in the previous step. Subsequently, the solvent was removed and the residue was dissolved in $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, evaporated and the free histamine base was dried *in vacuo*. To the residue was added 4-nitrophenol carbonate (16.5 g, 54.3 mmol) and CH_3CN (200 ml) and the resulting mixture was refluxed for 48 h. Subsequently, the solution was evaporated to dryness and the residue was purified by flash chromatography on a silica gel column using EtOAc/hexanes=1/1 (*v/v*) to $CHCl_3/CH_3OH$=19/1 (*v/v*) as eluents to give the desired compound as a white solid (5.5 g, 74%). m.p. 220–222°C; ν_{max} (KBr): 3204, 3134 (N-H), 1734 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 6.87 (s, 1H), 5.70 (s, 1H), 3.55 (td, *J* = 6.4, 2.6 Hz, 2H), 3.01 (t, *J* = 6.4 Hz, 2H) ppm; ^{1}H NMR (d^6-DMSO) δ 8.21 (s, 1H), 8.05 (s, 1H), 6.79 (s, 1H), 3.34 (td, *J* = 6.4, 2.6 Hz, 2H), 2.87 (t, *J* = 6.4 Hz, 2H) ppm; ^{13}C NMR (d^6-DMSO) δ 148.39, 134.00, 127.31, 124.65, 38.69, 19.29 ppm; MS (*m/z*): 138 (M^++1), 137 (M^+), 81 (100), 67, 54; HRMS: calcd. for $C_6H_7N_3O$ (M^+) 137.059, found 137.059.

1-Methyl-1H-4-histamine **(1)**: A mixture of compound **3** (5.2 g, 37.9 mmol) and $(CH_3)_2SO_4$ (5.7 g, 45.5 mmol) in DMF (100 ml) was stirred at 40°C for 24 h. Most of the solvent was removed and the residue was precipitated by the addition of Et_2O (100 ml). The resultant solid was filtered, washed with Et_2O, and dried *in vacuo*. ^{1}H NMR (d^6-DMSO) δ 9.65 (s, 1H), 9.03 (s, 1H), 7.57 (s, 1H), 3.87 (s, 3H), 3.45 (td, *J* = 6.4, 2.7 Hz, 2H), 3.36 (s, 3H), 3.00 (*t*, *J* = 6.4 Hz, 2H) ppm. The resulting quaternary salt **6** was dissolved in aqueous HCl (6M, 200 ml) and the mixture was refluxed overnight. After evaporating the solvent, the residue was treated with NaOH (6.0 g, 190 mmol) in CH_3OH (200 ml) with refluxing for 1h. Subsequently, the solvent was removed, the residue was dissolved in $CHCl_3$, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed and the residue was dried *in vacuo* to give the desired compound as a pale yellow liquid (3.8 g, 74%). ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 6.62 (s, 1H), 3.60 (s, 3H), 2.94 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 6.5, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 140.77, 137.20, 116.93, 41.79, 33.14, 32.11 ppm; MS (*m/z*): 127 (M^++2), 126 (M^++1), 125 (M^+), 124 (M^+-1), 108, 96, 81(100), 68, 54; HRMS: calcd. for $C_6H_{11}N_3$ (M^+) 125.095, found 125.095.

4-Hydroxyethyl-1-methyl-1H-imidazole **(7)**: To a mixture of compound **1** (1.0 g, 8.0 mmol) in AcOH (15 ml) and concd. HCl (2 ml) was added a solution of $NaNO_2$ (882 mg, 12.8 mmol) in water (5 ml) at 0°C. The resulting mixture was stirred at room temperature for 1 h and heated to 80°C with stirring for another 1h. The solvent was removed and the residue was refluxed with NaOH (1.2 g, 30 mmol) in CH_3OH (20 ml) for 1 h. After evaporating the solvent, the residue was dissolved in $CHCl_3$, dried over Na_2SO_4, filtered and purified by preparative layer chromatography on a silica gel plate using $CHCl_3$ (flushed with NH_3) as the eluent to give the desired compound as a pale yellow liquid (352 mg, 35%). ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 6.65 (s, 1H), 3.84 (t, *J* = 5.9 Hz, 2H), 3.61 (s, 3H), 2.75 (t, *J* = 5.9, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 140.58, 137.00, 116.81, 62.20, 33.19, 30.54 ppm; MS (*m/z*): 127 (M^++1), 126 (M^+), 125 (M^+-1), 111, 96 (100), 81, 68, 54; HRMS: calcd. for $C_6H_{10}N_2O$ (M^+) 126.079, found 126.079.

5-Oxo-2-phenacyl-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidinium bromide **(8)**: A mixture of compound **3** (2.0 g, 14.6 mmol) and 2-bromoacetophenon. (3.5 g, 17.5 mmol) in CH_3CN (50 ml) was refluxed for 24 h. The mixture was cooled to room temperature and filtered. The resultant white solid (4.3 g, 88%) was washed with $CHCl_3$ and Et_2O and dried *in vacuo* m.p. 204–206°C; ν_{max} (KBr): 3123, 3034 (N–H), 1752, 1699 (C = O) cm^{-1}; ^{1}H NMR (d^6-DMSO) δ 9.64 (s, 1H), 9.15 (s, 1H), 8.05–8.07 (m, 2H), 7.77–7.79 (m, 1H), 7.61–7.66 (m, 3H), 6.10 (s, 2H), 3.52 (t, *J*=6.4 Hz, 2H), 3.09 (t, *J* = 6.4 Hz, 2H) ppm; MS (*m/z*): 255, 199, 105 (100), 91, 77, 67; HRMS: calcd. for $C_{14}H_{14}{}^{79}BrN_3O_2$($M^+$) 335.027, found 335.027.

1-Phenacyl-1H-4-histamine t-*butoxycarbamate* **(9)**: A mixture of compound **8** (4.0 g, 11.9 mmol) and $^iPr_2NEt$ (3.1 g, 23.8 mmol) in *t*-BuOH (120 ml) was refluxed for 48 h. The solvent was removed and the residue was subjected to chromatography on a silica gel column using $CHCl_3$/hexanes = 2/1 (*v/v*) (flushed with NH_3) as the eluent to give the desired compound as a white solid (1.8 g, 46%). m.p. 102–104°C; ν_{max} (KBr): 3105 (N-H), 1696 (C = O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96–7.98 (m, 2H), 7.66 (m, 1H), 7.51–7.56 (m, 2H), 7.43 (s, 1H), 6.72 (s, 1H), 5.34 (s, 2H), 5.19 (s, 1H), 3.44 (t, *J* = 6.5 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 1.43 (s, 9H) ppm; MS (*m/z*): 329, 273, 256, 228, 212, 200, 105(100), 91, 77, 59; HRMS: calcd. for $C_{18}H_{23}N_3O_3$(M^+) 329.174, found 329.174.

3-Methyl-1-phenacyl-1H-4-histamine t-*butoxycarbamate imidazolium iodide* **(10)**: A mixture of compound **9** (1.6 g, 4.9 mmol) and CH_3I (6.9 g, 48.6 mmol) in acetone (50 ml) was stirred at 35°C for 24 h. The solvent was then evaporated and the residue was dried *in vacuo* to give the desired compound as a yellow semisolid (2.4 g, 100%). ^{1}H NMR (d^6-DMSO) δ 8.98 (s, 1H), 8.03–8.05 (m, 2H), 7.74–7.78 (m, 1H), 7.61–7.65 (m, 2H), 7.46 (s, 1H), 7.05 (m, 1H), 6.00 (s, 2H), 3.87 (s, 3H), 3.22 (m, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 1.39 (s, 9H) ppm; MS (*m/z*): 210, 149, 127, 105, 83(100), 59; HRMS: calcd. for $C_{19}H_{23}{}^{127}IN_3O_3$($M^+$) 471.098, found 471.102.

1-Methyl-1H-5-histamine t-butoxycarbamate **(11)**: A mixture of compound **10** (2.3 g, 4.9 mmol) and zinc powder (15.4 g, 235.6 mmol) in CH_3OH (40 ml) and AcOH (40 ml) was vigorously stirred in an ultrasonic bath for 24 h. The reaction mixture was filtered, the filtrate was concentrated and the residue was purified by chromatography on a silica gel column using $CHCl_3$/hexanes = 1/1 (*v/v*) (flushed with NH_3) as the eluent to give the desired compound

as a white solid (1.1 g, 100%). m.p. 42–44°C; ν_{max} (CCl_4): 3096 (N-H), 1686 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (s, 1H), 6.81 (s, 1H), 4.80 (s, 1H), 3.57 (s, 3H), 3.33 (m, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 155.80, 137.82, 128.99, 126.75, 79.19, 39.33, 31.14, 28.22, 24.42 ppm; MS (*m/z*): 225 (M^+), 184, 169, 152, 124, 108, 96 (100), 83, 68, 57; HRMS: calcd. for $C_{11}H_{19}N_3O_2(M^+)$ 225.148, found 225.148.

1-Methyl-1H-5-histamine **(2)**: A mixture of compound **11** (1.0 g, 4.4 mmol) in aqueous HCl (6M, 30 ml) was refluxed overnight. The solvent was removed and the residue was refluxed with NaOH (1.0 g, 25 mmol) in CH_3OH (50 ml) for 30 min. The reaction mixture was concentrated and the residue was dissolved in $CHCl_3$. The organic layer was dried over Na_2SO_4 and filtered. The solvent was removed and the residue was purified by preparative layer chromatography on a silica gel plate using $CHCl_3$ (flushed with NH_3) as the eluent to give the desired compound as a yellow liquid (280 mg, 50%). ^1H NMR ($CDCl_3$) δ 7.37 (s, 1H), 6.80 (s, 1H), 3.54 (s, 3H), 2.94 (t, *J* = 6.7 Hz, 2H), 2.68 (t, *J* = 6.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 137.53, 129.33, 126.46, 40.54, 31.05, 27.74 ppm; MS (*m/z*): 125 (M^+), 108, 96(100), 81, 68, 54; HRMS: calcd. for $C_6H_{11}N_3(M^+)$ 125.095, found 125.095.

meso-5,10,15,20-tetra(2′-aminophenyl)porphyrin 1-methyl-1H-4-histamine tetracarbamate **(13)**: To a solution of *meso*-5,10,15,20-tetra(2'-aminophenyl)porphyrin (**12**) (40 mg, 59 μmol) and Et_3N (60 mg, 590 μmol) in CH_2Cl_2 (30 ml) was added a solution of triphosgene (24 mg, 79 μmol) in CH_2Cl_2 (5 ml) under an atmosphere of N_2. The resulting mixture was stirred at room temperature for 1 h, after which a solution of compound **1** in CH_2Cl_2 (5 ml) was added. The mixture was stirred at room temperature overnight under an atmosphere of N_2. The solvent was evaporated and the residue was purified by preparative layer chromatography on a silica gel plate using $CH_3OH/CHCl_3$ = 1/19 (*v/v*) (flushed with NH_3) as the eluent to give the desired compound as a brown amorphous solid (46 mg, 61%). UV-Vis (λ_{max}, CH_2Cl_2): 422, 518 nm; ^1H NMR (d^6-DMSO) δ 8.70 (s, 8H), 8.31 (d, *J* = 8.0 Hz, 4H), 7.73–7.76 (m, 8H), 7.37 (td, *J* = 7.3, 1.5 Hz, 4H), 7.04 (s, 4H), 6.87 (s, 4H), 6.23 (s, 4H), 5.97 (m, 4H), 3.08 (s, 12H), 2.82 (*t*, *J* = 6.4 Hz, 8H), 2.06 (*t*, J=6.4 Hz, 8H), –2,75 (s, 2H) ppm; LIMS: calcd. for $C_{72}H_{70}N_{20}O_4(M^+)$ 1278.59, found 1278.59.

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