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Regiospecific Synthesis of 2,3-Disubstituted-L-Histidines and Histamines†

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Dedicated to the memory of Dr. Louis A. Cohen

Abstract—Regiospecific synthesis of 2,3-disubstituted-L-histidines and 2,3-disubstituted histamines starting from L-histidine methyl ester and histamine is reported. The key step involves homolytic free radical alkylation via silver catalyzed oxidative decarboxylation of alkylcarboxylic acids with ammonium persulfate.

With the increasing importance of enzymes and peptide hormones as targets for biological intervention, the synthetic derivatization of the genetically coded amino acids and their incorporation into peptides has become one of the attractive strategies for the preparation of hormone agonist/antagonists and enzyme inhibitors of pharmacological importance.[1] These synthetic building blocks of complex peptides are much more versatile for drug development. For example, they can circumvent the enzymatic degradation due to proteolysis, and thereby enhance the transport and absorption of peptide drugs.

On account of their implications in many physiological responses, histidine and histamine consisting of the aza aromatic imidazole ring are referred to collectively as bioimidazoles. Histidine is often an important amino acid at the active site of numerous enzymes, and appears to be essential for the recognition of peptide hormones by their receptors.[2] It is also known, for example, that the derivatized histidine containing peptides have a significant role in drug discovery.[3] On the other hand, involvement of histamine in a wide variety of physiological responses[4] including that for allergic and gastric manifestations have stimulated immense interest in the development of new synthetic methodologies for these novel bioimidazole derivatives.

Synthetic design of ring-substituted bioimidazoles, such as histidine and histamine is an arduous task that depends on the targeted ring position, and of these, the C-2 position presents the greatest challenge. Direct introduction of the alkyl group at the C-2 position of histidine or histamine by electrophilic substitution is not possible, because all electrophiles react preferentially at the C-5 position of the imidazole ring. Nucleophilic substitution on the imidazole ring is likewise a problem, requiring activation of the ring through placement of an electron withdrawing group on the ring. At the same time, the NH group of the ring requires selective protection, as the nucleophile would abstract the proton.

One of the major efforts of our laboratory has been the design and synthesis of novel ring-substituted-L-histidines for the purpose of obtaining highly potent thyrotropin-releasing hormone (TRH) analogues. Towards this end, we have previously reported general regiospecific synthetic routes to $N(1)^{\tau}$-alkyl-L-histidines and $N(1)^{\tau}$-alkyl histamines,[5] 2-substituted-L-histidines and 2-substituted histamines,[6] 1,2-disubstituted-L-histidines and 1,2-disubstituted histamines,[7] and more recently, an efficient and practical synthesis of ring-halogenated-L-histidines and ring-halogenated histamines.[8] We have demonstrated, as evident from reports,[6,7] that the synthesis of 2-alkyl and 1,2-dialkyl bioimidazoles could be efficiently achieved by direct regiospecific alkylation at the C-2 position of suitably protected histidine and histamine via silver catalyzed radical oxidative decarboxylation of alkylcarboxylic acids by ammonium persulfate in 10% H_2SO_4 as solvent based upon the

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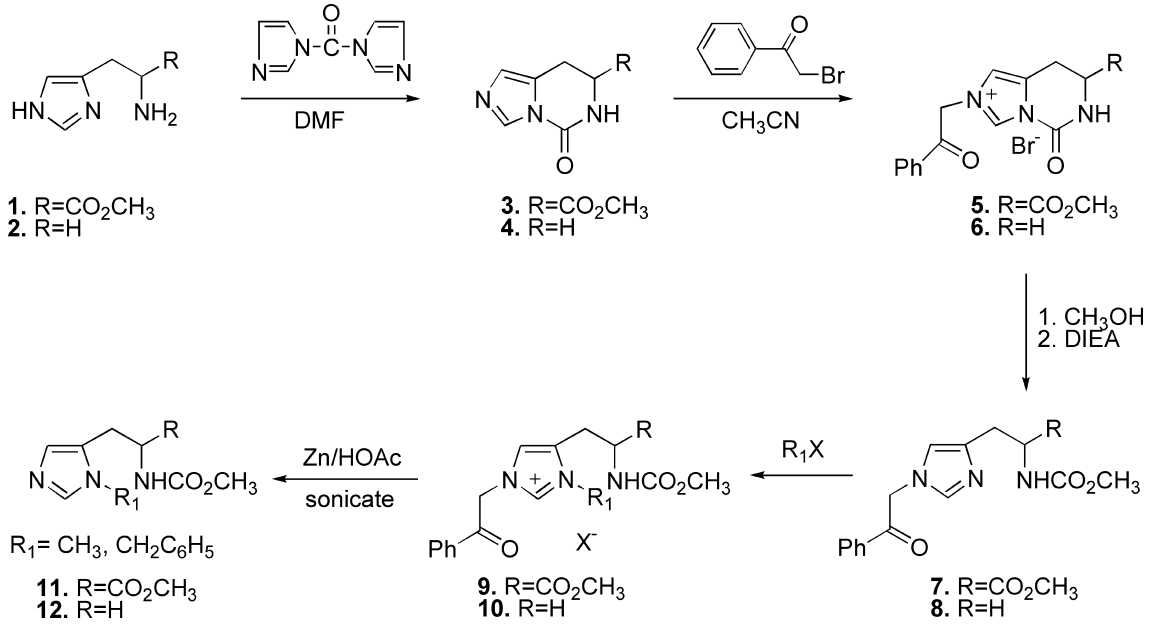
modifications of the procedures described by Minisci et al.[9] for the alkylation of aza heteroaromatics. As observed by us earlier, the method fails for more stable and less nucleophilic radicals such as aryl, heteroaryl and benzyl. However, it is the only method available for the direct regiospecific introduction of primary, secondary and tertiary alkyl groups of varying sizes at the C-2 position of the histidine and histamine. This communication describes the extension of these methodologies to include the first general route to hitherto unknown chiral 2,3-dialkyl-L-histidines and 2,3-dialkylhistamines (**15** and **16**).

Key intermediates 3-alkyl-α-carbomethoxy-L-histidines (**11**) and 3-alkyl-α-carbomethoxyhistamines (**12**) required for the synthesis of 2,3-disubstituted-L-histidines and 2,3-disubstituted histamines are synthesized according to Scheme 1.[10] Thus, 5,6,7,8-tetrahydro-5-oxoimidazo[1,5-*c*]pyrimidines (**3**, **4**), obtained by reacting **1** and **2** with 1,1′-carbonyl-diimidazole in DMF at 60 °C for 5–8 h, led to 2-phenacyl substituted quaternary salts **5** and **6**, on treatment with phenacyl bromide in acetonitrile under reflux conditions.[5,10] Compounds **5** and **6** on refluxing with methanol in the presence of *N,N*-diisopropylethylamine for 5 days gave fully protected 1-phencyl-*N*-α-carbomethoxy-L-histidine methyl ester (**7**) and 1-phencyl-*N*-α-carbomethoxyhistamine (**8**) (Scheme 1).[5,10,11] The latter compounds (**7** and **8**) on treatment with methyl iodide or benzyl bromide in acetonitrile at reflux temperature for 24 h gave the 1,3-dialkylated imidazolium quaternary compounds (**9** and **10**). No attempts were made to purify compounds **9** and **10** due to their extremely hygroscopic nature. However, crude **9** and **10** obtained by dropwise addition of their solutions in acetonitrile to vigorously stirred anhydrous ether, on treatment with glacial acetic acid/methanol (1:1) and zinc dust under ultra-sonication conditions provided 3-alkyl-*N*-α-carbomethoxy-L-histidines (**11**) and 3-alkyl-*N*-α-carbomethoxyhistamines (**12**) in 70–90% yield after column chromatography (EtOAc/CH_3OH, 95:5) (Scheme 1).

Homolytic radical alkylation of 3-alkyl-*N*-α-carbomethoxy-L-histidines (**11**) and 3-alkyl-*N*-α-carbomethoxyhistamines (**12**) with various commercially available alkylcarboxylic acids in the presence of ammonium persulfate and catalytic silver nitrate in 10% H_2SO_4 at 70 °C for 15 min readily provided protected 2,3-dialkyl bioimidazoles **13** and **14** in 12–45% yield (Table 1, Scheme 2).[12,13] Representative biologically important groups like *tert*-butyl, isopropyl, cyclohexyl and adamantyl were easily introduced at the C-2 position of the imidazole ring. As reported earlier, reaction is highly regiospecific in nature, with no apparent alkylation observed at the C-5 position of the imidazole ring.[5]

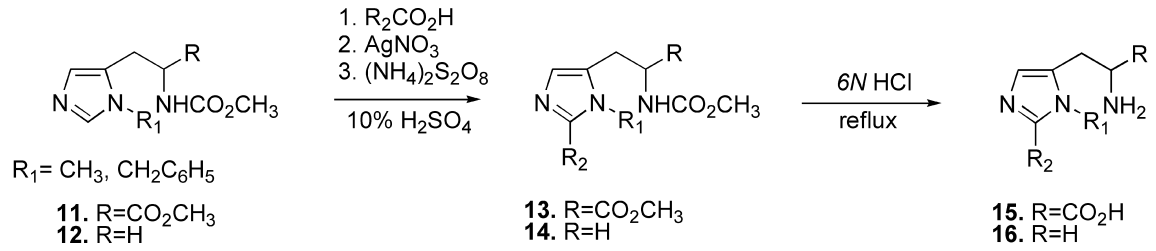


Scheme 1.

Table 1. C-2 alkylation of protected 3-alkyl-L-histidines and histamines

R_1	R_2	% Yield		% Yield		$[\alpha]_D^{25}$ (**15**)
		13	**14**	**15**	**16**	
a) CH_3	*c*-C_6H_{11}	43	nd[a]	80	nd	−15.2° (*c* = 1.0, H_2O)
b) CH_3	$C(CH_3)_3$	45	nd	85	nd	−23.7° (*c* = 1.2, H_2O)
c) $CH_2C_6H_5$	Adamantyl	12	15	95	89	−10.4° (*c* = 1.1, H_2O)
d) $CH_2C_6H_5$	*c*-C_6H_{11}	40	42	87	83	−7.9° (*c* = 1.25, H_2O)
e) $CH_2C_6H_5$	$CH(CH_3)_2$	42	44	82	91	−8.8° (*c* = 1, CH_3OH)
f) $CH_2C_6H_5$	$C(CH_3)_3$	45	43	85	90	−11.2° (c = 1, CH_3OH)

[a]nd (not done).



Scheme 2.

Compounds **13** and **14** were smoothly deprotected by reaction with 6 N HCl at reflux temperature to provide dihydrochloride salts of 2,3-dialkyl-L-histidines (**15**)[14,15] and 2,3-dialkylhistamines (**16**).[16] In the case of 2,3-dialkylhistidines the free amino acids were obtained by ion-exchange chromatography (Dowex, 50×2-200, H^+ form) after eluting the column with 15% NH_4OH, whereas the histamine derivatives were directly obtained by evaporation after acid hydrolysis.

Typical procedure for homolytic radical alkylation

A freshly prepared solution of ammonium persulfate (3 mmol) in water (10 mL) was added dropwise to a preheated (70 °C) mixture of **11** or **12** (1 mmol), silver nitrate (0.6 mmol) and alkylcarboxylic acid (2.5 mmol) in 10% H_2SO_4 (20 mL) during 10 min. The heating source was then removed and reaction proceeded with evolution of carbon dioxide. After 10 min, the reaction mixture was poured onto ice, and the resulting mixture was made alkaline with addition of 30% NH_4OH. This was extracted with ethyl acetate (4×50 mL), and the combined extracts were washed with NaCl solution (2×10 mL), dried over Na_2SO_4, and the solvent removed in vacuo to afford oil, which on flash column chromatography [EtOAc/CH_3OH, 95:5] over silica gel (230–400 mesh) gave **13** or **14** (Table 1).

The results summarized now establish the first direct regiospecific synthesis of previously inaccessible 2,3-disubstituted-L-histidines and 2,3-disubstituted histamines. The key to the synthesis is the free radical alkylation of the protonated 3-substituted bioimidazoles via silver catalyzed oxidative decarboxylation of acids with peroxydisulfate.

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12. Spectral data for *N*-carbomethoxy-2-*tert*-butyl-3-benzyl-L-histidine methyl ester (**13f**): mp 97–99 °C; IR (KBr), 3418, 2955, 1715, 1562, 1263; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H, 3×CH_3), 2.78 (t, 2H, CH_2, J=5.9 Hz), 3.64 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.48 (m, 1H, CH), 5.24 (bs, 1H, NH), 6.78 (s, 1H, 5-Ar-H), 6.86 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H); analysis for $C_{20}H_{27}N_3O_4$ (373.5), calcd C, 64.32; H, 7.29; N, 11.25; found C, 64.32; H, 7.25; N, 11.33; HRMS m/z 374 (M+1).
13. Spectral data for *N*-carbomethoxy-2-cyclohexyl-3-benzylhistamine (**14d**): mp 86–88 °C; IR (KBr), 3443, 2932, 2854, 1711, 1217, 756; ^1H NMR ($CDCl_3$) δ 1.24 (m, 4H, 2×CH_2), 1.73 (m, 6H, 3×CH_2), 2.52 (m, 2H, CH), 2.58 (m, 2H, CH_2), 3.62 (s, 3H, OCH_3), 5.80 (bs, 1H, NH), 5.08 (s, 2H, CH_2), 6.82 (s, 1H, 5-Ar-H), 6.88 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H); analysis for $C_{20}H_{27}N_3O_2$ (341.5), calcd C, 70.35; H, 7.97; N, 12.31; found C, 70.22; H, 7.65; N, 12.37; MS (EI) m/z 341 (M^+).
14. Spectral data for 2-*tert*-butyl-3-benzyl-L-histidine (**15f**): mp 217–219 °C (dec.); IR (KBr), 3387, 2981, 1738, 1409, 736; ^1H NMR (D_2O) δ 0.79 (m, 9H, 3×CH_3), 2.41 (m, 2H, CH_2), 3.28 (m, 1H, CH), 4.98 (s, 2H, CH_2), 6.38 (d, 2H, Ar-H), 6.72 (m, 2H, Ar-H), 6.78 (s, 1H, 5-Ar-H); analysis for $C_{17}H_{23}N_3O_2$ (301.4), calcd C, 67.75; H, 7.69; N, 13.94; found C, 67.80; H, 7.55; N, 13.50; HRMS m/z 302 (M+1); $[\alpha]_D^{25}$ −11.2° (c=1, CH_3OH). TLC system A (nBuOH/AcOH/H_2O, 2:1:1), R_f=0.6 (one spot); TLC system B (EtOAc/nBuOH/AcOH/H_2O, 2:1:1:1), R_f=0.55 (one spot).
15. The optical purity of modified histidine analogues were assessed on HPLC using CHIRALPAK WH chiral column

(ID 0.46 cm, particle size 10 μm), and results indicate presence of $\leqslant 0.8\%$ of the D-enantiomer in all cases.

16. Spectral data for 2-cyclohexyl-3-benzylhistamine dihydrochloride (**16d**): mp 203–205 °C (dec.); IR (KBr), 3390, 1405; ^{1}H NMR (D_2O) δ 0.59 (m, 10H, $5\times CH_2$), 2.08 (t, 2H, CH_2, $J = 7.4$ Hz), 2.23 (m, 2H, CH_2), 4.55 (s, 2H, CH_2), 6.19 (d, 2H, Ar-H), 6.73 (m, 3H, Ar-H), 6.82 (s, 1H, 5-Ar-H); analysis for $C_{18}H_{25}N_3 \cdot 2HCl$ (356.3), calcd C, 60.67; H, 7.63; N, 11.79; found C, 60.88; H, 7.67; N, 12.01; HRMS m/z 284 (M + 1).