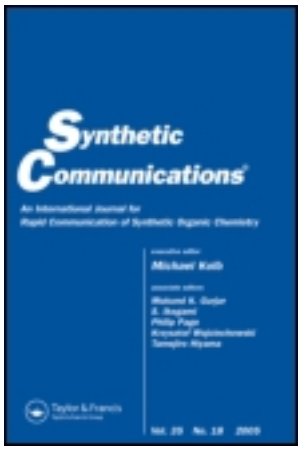

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Trityl-Directed Regiospecific Synthesis of 2,3-Disubstituted Bioimidazoles

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Trityl-Directed Regiospecific Synthesis of 2,3-Disubstituted Bioimidazoles[#]

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ABSTRACT

We report an efficient trityl-directed regiospecific synthesis of 2,3-disubstituted-L-histdines and 2,3-disubstituted histamines starting from α-*N*-trifluoroacetyl-L-histidine methyl ester and α-*N*-trifluoroacetylhistamine respectively in five steps.

Key Words: Bioimidazoles; Homolytic free-radical reaction; Trityl.

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INTRODUCTION

The continuing interest in design, synthesis, and use of non-proteinogenic α-amino acids as building blocks in the design and synthesis of bioactive peptides and peptidomimetics has led to intense efforts aimed at discovering new synthetic methodologies for these compounds. The use of the ring-substituted histidines as substrate for the synthesis of bioactive peptides,[1] and diverse biological activities of ring-substituted histamines[2] has appealed to several research groups including our own. However, to a large extent, the access to these important classes of compounds are restricted due to lack to credible synthetic methodologies. Over the years, the research efforts of our group are directed towards this end, and we have successfully reported synthesis of several novel ring-substituted bioimidazoles such as histidine and histamine.[3–6]

RESULTS AND DISCUSSION

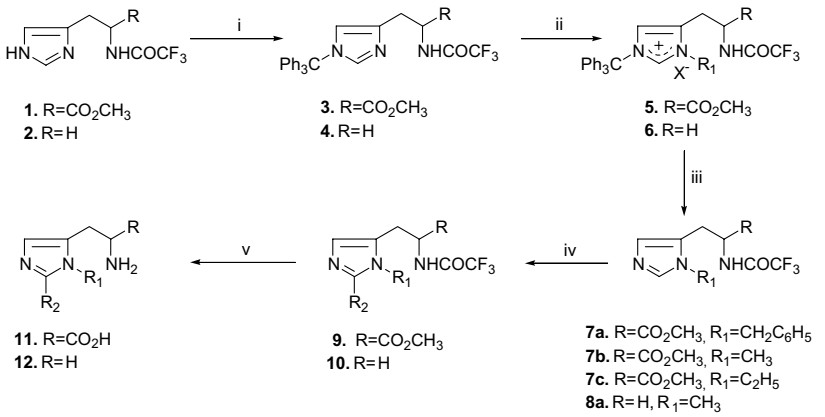
We have recently utilized phenacyl group as the protection for N-1(τ) position of the imidazole ring, and that resulted in the first synthesis of 2,3-disubstituted L-histidines and histamines.[7] This synthetic strategy consists of phencayl-directed regiospecific N-3(π) alkylation to provide protected 3-substituted L-histidines and histamines, which upon homolytic free radical alkylation led to successful realization of 2,3-disubstituted L-histidines and histamines. The protection of N-1(τ) position of the imidazole nucleus was required, because ring exists in two tautomeric forms, and it is commonly known that direct ring alkylation almost always results in a mixture of τ(1) and π(3) derivatives. Although, the τ derivative is often the major product, it is rarely exclusive. Only two classes of reagents, the halonitrobenzenes[8] and triarylmethyl halides[9–10] are found to give exclusively τ products. This clearly indicates that specific alkylation at the π nitrogen requires protection of the τ nitrogen, in addition to that of the side-chain functions.

Although, we have reported the first and only report on the synthesis of 2,3-disubstituted L-histidines and histamines, we conclude that this methodology suffers due to following disadvantages: (a) selective N-1(τ) protection of the imidazole ring by phenacyl group was achieved in three steps that also requires use of expensive 1,1′-carbonyl-diimidazole; (b) the intermediate imidazolium quaternary compounds were found to be highly hygroscopic, and attempts towards their isolation

and purification were not successful; (c) regiospecific N-3(π) alkylation of the imidazole ring was achieved in five steps; (d) and finally, this seven-step methodology had provided low-overall yield of the desired histidine and histamine analogues.[7]

As a continuation of our search for easy availability of novel ring-substituted bioimidazoles, this article describes an efficient and practical synthetic route to 2,3-disubstituted L-histidines and histamines in five steps. This alternate shorter strategy involves successful utilization of triphenylmethyl group (trityl, Trt) for the protection of the N-1(τ) nitrogen of the imidazole ring. In addition to the easy introduction in one step in excellent yield, the trityl group was efficiently and cleanly removed from τ nitrogen of the imidazole ring under very mild conditions using glacial acetic acid at ambient temperature.[10] However, the most important aspect of the use of trityl protection was the realization of the regiospecific N-3 substitution in three steps (Sch. 1) as compared to five-steps in the case of phenacyl-directed N-3 substitution of the imidazole ring.[7]

Thus, α-*N*-trifluoroacetyl-L-histidine methyl ester (**1**) and α-*N*-trifluoroacetylhistamine (**2**) on reaction with triphenylmethyl chloride and triethylamine in anhydrous benzene at reflux temperature for 1 h provided the exclusive N-1(τ)-trityl group protected analogues (**3** and **4**) in excellent yield (Sch. 1). The latter compounds **3–4** on treatment with various commercially available alkyl halides in chloroform at



Scheme 1. Reagents and conditions: (i) Ph_3CCl, NEt_3, C_6H_6, reflux; (ii) R_1X, $CHCl_3$, rt, 20 h; (iii) AgOAc, HOAc, 24–48 h; (iv) R_2CO_2H, $AgNO_3$, $(NH_4)_2S_2O_8$, 10% H_2SO_4, 70°C; (v) 6 N HCl, reflux, 8 h.

Table 1. Yields and $[\alpha]_D$ of 2,3-dialkylated bioimidazole derivatives.

			Yield (%)		Yield (%)		
No.	R_1	R_2	**9**	**10**	**11**	**12**	$[\alpha]_D^{25}$ (**11**)
a	$CH_2C_6H_5$	$C(CH_3)_3$	48	45	95[7]	88[7]	-11.9° ($c=1$, H_2O)
b	$CH_2C_6H_5$	*c*-C_5H_9	44	38	90	90	-8.5° ($c=1$, H_2O)
c	$CH_2C_6H_5$	*c*-C_4H_7	39	35	85	92	-10.4° ($c=1$, H_2O)
d	$CH_2C_6H_5$	*c*-C_3H_5	21	19	88	95	-7.2° ($c=1$, H_2O)
e	$CH_2C_6H_5$	$CH(CH_3)_2$	35	nd[a]	95[7]	nd	-9.7° ($c=1$, H_2O)
f	CH_3	*c*-C_5H_9	47	nd	88	nd	-19.8° ($c=1.1$, H_2O)
g	C_2H_5	*c*-C_5H_9	42	nd	85	nd	-22.3° ($c=1.2$, H_2O)

[a]Nd (not done).

ambient temperature for 20 h afforded corresponding imidazolium quaternary salts (**5–6**). These imidazolium salts (**5–6**) were found to be highly hygroscopic and every attempt towards their isolation proved to be unsuccessful. Thus, crude salts **5–6** upon deprotection with glacial acetic acid in the presence of silver acetate for 24–48 h provided α-*N*-trifluoroacetyl-3-alkyl-L-histidine methyl ester (**7**) and α-*N*-trifluoroacetyl-3-alkylhistamine (**8**) in 60–88% yield. Compounds **7–8** on homolytic free radical reaction with various commercially available alkylcarboxylic acids in the presence of ammonium persulfate and silver nitrate in 10% H_2SO_4 readily provided fully protected α-*N*-trifluoroacetyl-2,3-dialkyl-L-histidine methyl esters (**9**) and α-*N*-trifluoroacetyl-2,3-dialkylhistamines (**10**). As described by Jain et al. earlier,[4,5,7] the reaction proceeds via silver catalyzed free radical oxidative decarboxylation of alkylcarboxylic acids by ammonium persulfate in 10% sulfuric acid as solvent. Reaction is highly regiospecific,[11] and groups such as cyclopropyl, cyclopentyl, and *tert*-butyl are easily introduced in 19–48% yields (Table 1). In all cases, the 2,3-dialkyl-L-histidines (**11**) and 2,3-dialkylhistamines (**12**) were obtained by the deprotection of **9** and **10** with refluxing 6 N HCl, followed by ion-exchange chromatography (Dowex, 50×2–200, H^+ form) for the amino acids; whereas, histamine derivatives were isolated as their hydrochloride salts by evaporation of the acid hydrolysis solution.

In conclusion, this communication describes a facile trityl-directed synthesis for 2,3-disubstituted bioimidazoles in five-step, each of which in good yields, and that is more efficient and affordable compared to phenacyl-directed approach for 2,3-disubstituted bioimidazoles reported by us earlier.

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EXPERIMENTAL

Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained on Bruker Avance DPX (300 MHz) spectrometer using TMS as internal reference. Chemical Ionization (CI) mass spectra were recorded on Shimadsu GCMS-QP 5000 spectrometer using methane as carrier reagent gas. Electron Spray Ionization (ESI) spectra were recorded on a LCMS Finnigan Mat LCQ spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 MC Polarimeter. Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F_{254}, 0.2 mm thickness) sheets.

Synthesis of α-*N*-Trifluoroacetyl-1-trityl-L-histidine Methyl Ester (3) and α-*N*-Trifluoroacetyl-1-tritylhistamine (4)

A mixture of triphenylmethyl chloride (10 mmol), α-*N*-trifluoroacetyl-L-histidine methyl ester (**1**, 10 mmol) or α-*N*-trifluoroacetylhistamine (**2**, 10 mmol), and triethylamine (10 mmol) in anhydrous benzene (50 mL) was heated at reflux for 1 h. Reaction mixture was cooled, filtered, and the solvent was evaporated to yield compounds (**3–4**) as off white solid.

α-*N*-Trifluoroacetyl-1-trityl-L-histidine methyl ester (3). Yield: 92%; m.p. 102–104°C. ^{1}H NMR ($CDCl_3$): δ 3.15 (m, 2H, CH_2), 3.67 (s, 3H, CH_3), 4.83 (m, 1H, CH), 6.65 (s, 1H, 5-Ar-H), 7.21 (m, 15H, Ar-H), 7.56 (s, 1H, 2-Ar-H). Anal. calcd.: C, 66.27; H, 4.77; N, 8.28. Found: C, 66.22; H, 4.77; N, 8.25. ESIMS: m/z 508 (M + 1).

α-*N*-Trifluoroacetyl-1-tritylhistamine (4). Yield: 95%; m.p. 120–123°C. ^{1}H NMR ($CDCl_3$): δ 2.78 (m, 2H, CH_2), 3.66 (m, 2H, CH_2), 6.61 (s, 1H, 5-Ar-H), 7.24 (m, 15H, Ar-H), 7.39 (s, 1H, 2-Ar-H). Anal. calcd.: C, 69.48; H, 4.93; N, 9.35. Found: C, 69.44; H, 4.90; N, 9.29. ESIMS: m/z 450 (M + 1).

General Procedure for the Synthesis of α-*N*-Trifluoroacetyl-3-alkyl-L-histidine Methyl Esters (7) and α-*N*-Trifluoroacetyl-3-alkylhistamines (8)

A mixture of α-*N*-trifluoroacetyl-1-trityl-L-histidine methyl ester (**3**, 1 mmol) or α-*N*-trifluoroacetyl-1-tritylhistamine (**4**, 1 mmol) and alkyl

halide (1.2 mol) in chloroform (2 mL) was stirred at room temperature for 20 h. The solvent was evaporated and residue was added to cold vigorously stirred diethyl ether (25 mL). The solvent removed by filtration to yield the imidazolium quaternary salts **5–6**. To the solution of the imidazolium salt (**5–6**) in glacial acetic acid (10 mL) was added silver acetate (1 mmol) and reaction mixture was stirred for 24–48 h at ambient temperature. Filtered, solvent was evaporated, and the resulting residue was basified with 10% aqueous sodium carbonate solution. Extracted with CH_2Cl_2 (2×25 mL), dried (Na_2SO_4), and solvent removed in vacuo. The resulting residue upon purification by column chromatography provided compounds (**7–8**).

α-*N*-Trifluoroacetyl-3-benzyl-L-histidine methyl ester (7a). Yield: 75%; m.p. 130–135°C. ^{1}H NMR ($CDCl_3$): δ 3.17 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 4.69 (m, 1H, CH), 5.15 (s, 2H, CH_2), 6.94 (s, 1H, 5-Ar-H), 7.11 (m, 2H, Ar-H), 7.37 (m, 3H, Ar-H), 7.52 (s, 1H, 2-Ar-H). Anal. calcd.: C, 54.09; H, 4.54; N, 11.83. Found: C, 54.13; H, 4.60; N, 11.77. ESIMS: m/z 356 (M + 1).

α-*N*-Trifluoroacetyl-3-methyl-L-histidine methyl ester (7b). Yield: 65%; m.p. 98–99°C. ^{1}H NMR ($CDCl_3$): δ 3.10 (m, 2H, CH_2), 3.63 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.81 (m, 1H, CH), 6.67 (s, 1H, 5-Ar-H), 7.39 (s, 1H, 2-Ar-H). Anal. calcd.: C, 43.02; H, 4.33; N, 15.05. Found: C, 43.20; H, 4.55; N, 14.89. ESIMS: m/z 280 (M + 1).

α-*N*-Trifluoroacetyl-3-ethyl-L-histidine methyl ester (7c). Yield: 60%; m.p. 88–90°C. ^{1}H NMR ($CDCl_3$): δ 1.50 (t, 3H, CH_3), 3.15 (m, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.99 (t, 2H, CH_2), 4.75 (m, 1H, CH), 6.68 (s, 1H, 5-Ar-H), 7.38 (s, 1H, 2-Ar-H). Anal. calcd.: C, 45.05; H, 4.81; N, 14.33. Found: C, 45.27; H, 4.59; N, 14.21. ESIMS: m/z 294 (M + 1).

α-*N*-Trifluoroacetyl-3-benzylhistamine (8a). Yield: 88%; m.p. 111–113°C. ^{1}H NMR ($CDCl_3$): δ 2.75 (m, 2H, CH_2), 3.58 (m, 2H, CH_2), 4.77 (m, 1H, CH), 4.99 (s, 2H, CH_2), 6.96 (s, 1H, 5-Ar-H), 7.07 (m, 3H, Ar-H), 7.14 (m, 2H, Ar-H), 7.32 (s, 1H, 2-Ar-H). Anal. calcd.: C, 56.56; H, 4.75; N, 14.14. Found: C, 56.44; H, 4.67; N, 14.33. ESIMS: m/z 298 (M + 1).

Typical Procedure for the Synthesis of 2,3-Dialkyl-L-histidines (11) and 2,3-Dialkylhistamines (12)

α-*N*-Trifluoroacetyl-3-alkyl-L-histidine methyl ester (**7**, 1 mmol) or α-*N*-trifluoroacetyl-3-alkylhistamine (**8**, 1 mmol), was added to a mixture of silver nitrate (0.6 mmol) and alkylcarboxylic acid (2.5 mmol) in 10% H_2SO_4 (10 mL), and the reaction mixture was heated at 70°C. A freshly

prepared solution of ammonium persulfate (3 mmol) in water (5 mL) was added drop wise over 15 min. The heating source was removed and the reaction proceeded with evolution of carbon dioxide. After 15 min, the reaction was terminated by pouring it onto ice. The resulting mixture was made alkaline with 25% NH_4OH solution and extracted with ethyl acetate (3×25 mL). The combined extracts were washed with brine (2×5 mL) and dried (Na_2SO_4). The solvent was removed in vacuo to afford oil, which on chromatography over silica [ethyl acetate/hexanes (8:2)] provided compounds (**9–10**) in 19–48% yield (Table 1). A solution of **9** or **10** (1 mmol) in 6 N HCl (10 mL) was heated at reflux for 8 h. The dihydrochloride salts of the 2,3-dialkyl-L-histidines (**11**) and 2, 3-dialkyl-histamines (**12**) were obtained directly by evaporation of the acid hydrolysis solutions. A solution of the 2,3-dialkyl-L-histidine dihydrochloride (**11**) in water (5 mL) was applied to an ion-exchange column (Dowex 50×2–200, H^+ form). The column was eluted with water until neutral to pH paper. The amino acid was eluted with 10% NH_4OH solution. Evaporation of solvent afforded the free crystalline amino acids **11**.[12]

2-Cyclopentyl-3-benzyl-L-histidine (11b). M.p. 212–214°C. ^{1}H NMR (D_2O): δ 1.73 (s, 4H, CH_2), 2.14 (m, 4H, CH_2), 2.48 (m, 1H, CH), 3.01 (m, 2H, CH_2), 4.18 (m, 1H, CH), 5.49 (s, 2H, CH_2), 7.03 (s, 1H, 5-Ar-H), 7.29 (m, 3H, Ar-H), 7.46 (m, 2H, Ar-H). Anal. calcd.: C, 68.98; H, 7.40; N, 13.41. Found: C, 67.00; N, 7.53; N, 13.22. CIMS: m/z 314 (M + 1).

2-Cyclobutyl-3-benzyl-L-histidine (11c). M.p. 205–209°C. ^{1}H NMR (D_2O): δ 1.83 (m, 6H, CH_2), 2.31 (m, 1H, CH), 2.94 (m, 2H, CH_2), 4.21 (m, 1H, CH), 5.29 (s, 2H, CH_2), 6.88 (s, 1H, 5-Ar-H), 7.09 (m, 3H, Ar-H), 7.36 (m, 2H, Ar-H). Anal. calcd.: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.12; N, 7.30; N, 13.88. CIMS: m/z 300 (M + 1).

2-Cyclopropyl-3-benzyl-L-histidine (11d). M.p. 199–202°C. ^{1}H NMR (D_2O): δ 1.56 (m, 4H, CH_2), 2.66 (s, 1H, CH), 3.15 (m, 2H, CH_2), 4.10 (m, 1H, CH), 5.51 (s, 2H, CH_2), 7.14 (s, 1H, 5-Ar-H), 7.34 (m, 3H, Ar-H), 7.52 (s, 2H, Ar-H). Anal. calcd.: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.25; N, 7.85; N, 14.99. CIMS: m/z 386 (M + 1).

2-Cyclopentyl-3-methyl-L-histidine (11e). M.p. 216–219°C. ^{1}H NMR (D_2O): δ 1.53 (m, 4H, CH_2), 1.83 (m, 4H, CH_2), 2.82 (m, 1H, CH), 2.95 (m, 2H, CH_2), 3.67 (s, 3H, CH_3), 3.88 (m, 1H, CH), 6.99 (s, 1H, 5-Ar-H). Anal. calcd.: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.55; N, 7.99; N, 17.92. CIMS: m/z 238 (M + 1).

2-Cyclopentyl-3-ethyl-L-histidine (11f). M.p. 202–205°C. ^{1}H NMR (D_2O): δ 1.55 (m, 7H, CH_3, CH_2), 1.85 (m, 4H, CH_2), 2.75 (m, 1H, CH), 2.93 (m, 2H, CH_2), 3.89 (q, 2H, CH_2), 3.99 (m, 1H, CH), 6.87 (s, 1H, 5-Ar-H). Anal. calcd.: C, 61.13; H, 8.42; N, 16.72. Found: C, 61.42; N, 8.67; N, 16.99. CIMS: m/z 252 (M+1).

2-Cyclopentyl-3-benzylhistamine dihydrochloride (12b). M.p. 188–191°C. ^{1}H NMR (D_2O): δ 1.89 (m, 8H, CH_2), 2.54 (m, 2H, CH_2), 2.83 (m, 3H, CH_2 and CH), 5.21 (s, 2H, CH_2), 6.88 (s, 1H, 5-Ar-H), 7.31 (m, 3H, Ar-H), 7.56 (m, 2H, Ar-H). Anal. calcd.: C, 59.65; H, 7.36; N, 12.28. Found: C, 59.33; H, 7.09; N, 12.44. ESIMS: m/z 270 (M + 1).

2-Cyclobutyl-3-benzylhistamine dihydrochloride (12c). M.p. 185–189°C. ^{1}H NMR (D_2O): δ 1.99 (m, 6H, CH_2), 2.64 (m, 2H, CH_2), 2.97 (m, 3H, CH_2 and CH), 5.17 (s, 2H, CH_2), 6.93 (s, 1H, 5-Ar-H), 7.33(m, 3H, Ar-H), 7.52 (m, 2H, Ar-H). Anal. calcd.: C, 58.54; H, 7.06; N; 12.80. Found: C, 58.55; H, 7.17; N, 12.89. ESIMS: m/z 256 (M + 1).

2-Cyclopropyl-3-benzylhistamine dihydrochloride (12d). M.p. 182–184°C. ^{1}H NMR (D_2O): δ 1.96 (m, 4H, CH_2), 2.57 (m, 2H, CH_2), 2.99 (m, 3H, CH_2 and CH), 5.09 (s, 2H, CH_2), 6.83 (s, 1H, 5-Ar-H), 7.37 (m, 3H, Ar-H), 7.59 (m, 2H, Ar-H). Anal. calcd.: C, 57.33; H, 6.74; N; 13.37. Found: C, 57.54; H, 7.03; N, 13.55. ESIMS: m/z 242 (M + 1).

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12. The optical purity of all ring-modified histidine analogues was assessed on HPLC using CHIRALPAK WH chiral column (ID 0.46 cm, particle size 10 μm), and results indicate presence of ≤1% of the D-enatiomer in all cases.

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