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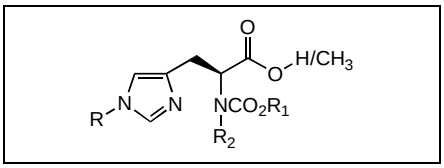
Received September 7, 2006



Two diverse methodologies describe the first synthesis of suitably protected *N*-α,*N*-1(τ)-dialkyl-L-histidine derivatives. Synthesis of suitably protected *N*-α,*N*-1(τ)-dialkyl-L-histidines **7**-**9** containing different alkyl groups at the *N*-α and *N*-1(τ) positions was achieved in four steps starting from L-histidine methyl ester. Whereas, in the one-step alternate route *N*-α-Boc-L-histidine methyl ester upon direct and simultaneous *N*-α and *N*-1(τ) alkylation with various alkyl halides in the presence of sodium hydride in DMF easily afforded *N*-α,*N*-1(τ)-dialkyl-L-histidines **14** containing identical alkyl group at the *N*-α and *N*-1(τ) positions in high yields. Both procedures allowed facile entry to methyl and other higher alkyl groups at the *N*-α-position of the histidine ring

J. Heterocyclic Chem., **44**, 1265 (2007).

INTRODUCTION

Backbone modification by conformational restriction of amide bond is an attractive strategy to obtain useful information about bioactive conformation of peptides [1, 2]. Such modifications introduce local backbone constraints, *e.g*. *N*-α-alkylation greatly limits the ϕ torsional angle that restricts the affected residue and the amino acid preceding it to an extended conformation [3], eliminates the potential intramolecular hydrogen bonding capability of the amide bond nitrogen, increase resistance to proteolytic enzymes cleavage sites and also the hydrophobicity of the peptide [4]. Incorporation of *N*-α-methyl amino acid in a peptide ligand has often been found to increase their potency or selectivity and resulting peptoids are increasingly recognized as potentially useful therapeutics. For example, in one such study conducted recently, potential effects of *N*-α-methylation of peptide bond NH groups on binding affinity and receptor subtype specificity of synthetic analogues of somatostatin octapeptide agonist and antagonist was examined, and some analogues displayed greatly enhanced affinity and specificity [5–7].

Synthetic design of modified histidine derivatives is a tedious task due to the basic and high nucleophilic character of the imidazole ring at the side chain. One of the major efforts of our laboratory has been the design and synthesis of novel derivatized L-histidines and we have previously reported syntheses for some of these scaffolds [8–15]. Recently, our requirement of *N*-α,*N*-1(τ)-dialkyl-L-histidines [16] as components of antimicrobial and CNS selective peptide analogues created a need for these building blocks in suitably protected forms for incorporation into the target peptoids by solid-phase synthesis. Although, a range of synthetic methods have been employed to prepare *N*-α-methyl amino acids [17], none are easily adapted for the synthesis of *N*-α-alkylated histidines suitable for solid phase peptide synthesis. More recently, a unified synthetic procedure for the twenty natural amino acids through the generation of intermediate 5-oxazolidinone and its subsequent transformation to *N*-α-methyl derivative by reductive cleavage in the presence of triethylsilane in trifluoroacetic acid (TFA) was reported [18, 19]. This procedure provides *N*-α-methyl-L-histidine derivative protected with *N*-α-carbobenzyloxy (Cbz) and *N*-1(τ)-dinitrophenyl (DNP) groups in six overall steps. However, due to the use of acidic conditions in several of the synthetic steps, we concluded that the procedure is not useful for the preparation of *tert*-butoxycarbonyl (*t*-Boc) group protected *N*-α-alkyl-L-histidines required for *t*-Boc solid-phase peptide synthesis protocol [20]. Furthermore, 5-oxazolidinone intermediate based synthetic methodology could not be applied to synthesize *N*-α,*N*-1(τ)-dialkyl groups containing L-histidines. In continuation of our search for easy availability of novel modified L-histidines, this article describes two efficient synthetic routes to *N*-α,*N*-1(τ)-dialkyl-L-histidines.

RESULTS AND DISCUSSION

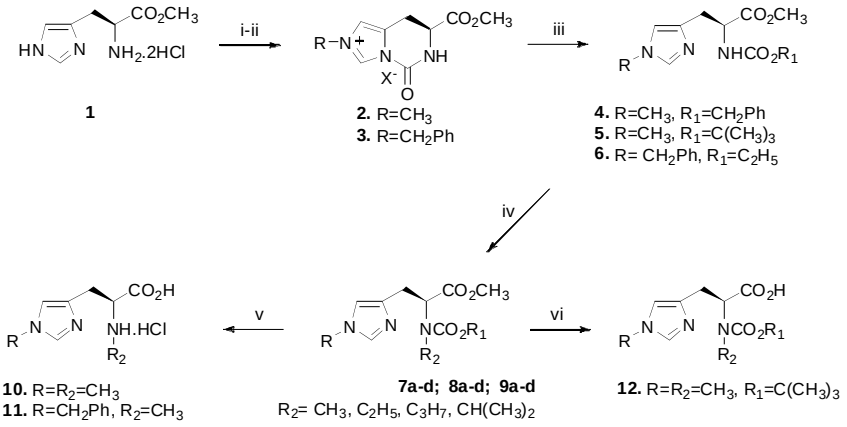
We have earlier reported a facile synthesis of *N*-1(τ)-alkyl-L-histidines *via* a quaternary imidazolium salt intermediate [8]. We utilized this procedure to achieve our objective of synthesizing fully protected *N*-1(τ)-alkyl-L-histidine intermediates required for target amino acids. Reaction of commercial L-histidine methyl ester

dihydrochloride with 1,1'-carbonyl-diimidazole in DMF provided the cyclic urea, which upon alkylation with methyl iodide or benzyl bromide in refluxing CH_3CN for 16 h provided quaternary imidazolium salts **2–3** in excellent yields (Scheme 1) [8]. The imidazolium salts **2–3** were then reacted with an alcohol in the presence of *N,N*-diisopropylethylamine at reflux temperature for 2–4 days, to give fully protected *N*-1(τ)-alkyl-L-histidine deriveatives **4–6** [8,21,22]. Reaction of the latter compounds **4–6** with NaH at ambient temperature for 30 min in anhydrous DMF under nitrogen atmosphere, followed by addition of the appropriate commercially available alkyl iodides and stirring for 4 h readily afforded fully protected *N*-α,*N*-1(τ)-dialkyl-L-histidines **7–9**.

The reaction allows easy entry to not only *N*-α-methyl-L-histidine derivatives, but also to higher alkyl groups such as ethyl, *n*-propyl and *i*-propyl containing L-histidines (Table 1), and can also be conveniently adapted to include many other alkyl groups. The *N*-α,*N*-1(τ)-dialkyl-L-histidines were obtained by the deprotection of **7a** and **8a** with refluxing solution of them in 6 *N* HCl. Evaporation of the solution produced the amino acid hydrochlorides **10–11** respectively. Selective deprotection of compounds **8a** in the presence of $LiOH.H_2O$ in a mixture of H_2O-MeOH at ambient temperature for 30 min afforded *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine **12**, suitable for *t*-Boc solid-phase peptide synthesis methodology (Scheme 1).

A shorter one-step route which provides *N*-α,*N*-1(τ)-dialkyl-L-histidines containing identical alkyl group was then devised. Accordingly, commercially available *N*-α-Boc-L-histidine methyl ester **13** upon direct ring N-1(τ) and side chain α-position alkylation with methyl iodide or ethyl iodide in the presence of NaH in DMF for 12 h at ambient temperature cleanly afforded *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester **8a** and *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-diethyl-L-histidine methyl ester **14a** in excellent yields. However, the method was found to provide unreacted starting material and some unidentifiable products when it was tried with benzyl bromide. Alternatively, *N*-α-Boc-L-histidine methyl ester **13** upon reaction with benzyl bromide in the presence of NaH in DMF at 80 °C for 10 h produced *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dibenzyl-L-histidine methyl ester **14b** in 61% yield (Scheme 2). Fully deprotected amino acids, *N*-α,*N*-1(τ)-diethyl-L-histidine hydrochloride **15a** and *N*-α,*N*-1-dibenzyl-L-histidine hydrochloride **15b** were obtained by the deprotection of **14a** and **14b** with refluxing solution of them in 6 *N* HCl. Evaporation of the solution produced the amino acid hydrochlorides **15a–b** as described earlier.

The results summarized establish the first synthesis of previously inaccessible *N*-α,*N*-1(τ)-dialkyl-L-histidines. Two diverse and facile synthetic methodologies which produce different or identical *N*-α and *N*-1(τ) alkyl groups containing L-histidines are described herein. These methodologies allowed easy access to *N*-α-Boc-*N*-α,*N*-1(τ)-dimethyl-L-histidines required by us for solid-phase peptide synthesis and were conveniently extended to introduce a diverse range of higher primary and secondary alkyl groups.



1

2. R=CH_3
3. R=CH_2Ph

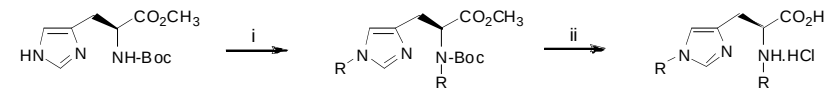
4. R=CH_3, R_1=CH_2Ph
5. R=CH_3, R_1=$C(CH_3)_3$
6. R= CH_2Ph, R_1=C_2H_5

10. R=R_2=CH_3
11. R=CH_2Ph, R_2=CH_3

7a-d; 8a-d; 9a-d
R_2= CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$

12. R=R_2=CH_3, R_1=$C(CH_3)_3$

Scheme 1. *Reagents and conditions:* i. CDI, DMF, 60 °C, 8 h; ii. RX, CH_3CN, reflux, 16 h; iii. R_1OH, DIEA, reflux, 48-96 h; iv. R_2I, NaH, DMF, rt, 4 h; v. 6N HCl, 100 °C, 8 h; vi. $LiOH.H_2O$, CH_3OH, rt, 30 min.



13

8a, 14a-b
R = CH_3, C_2H_5, $CH_2C_6H_5$

10, 15a-b

Scheme 2. *Reagents and conditions:* i. CH_3I/C_2H_5I, NaH, DMF, rt, 12 h or $C_6H_5CH_2Br$, NaH, DMF, 80 °C, 10 h; ii. 6N HCl, 100 °C, 8 h

Table 1

Physical data of *N*-α,*N*-1(τ)-dialkyl-L-histidine methyl esters **7**-**9** and **14**

Product	R	R_1	R_2	% Yield	$[\alpha]^{D}_{25}$
7a	CH_3	$CH_2C_6H_5$	CH_3	84	+10.5 (*c* 1, $CHCl_3$)
7b	CH_3	$CH_2C_6H_5$	C_2H_5	62	+8.2 (*c* 1, $CHCl_3$)
7c	CH_3	$CH_2C_6H_5$	C_3H_7	17	+7.9 (*c* 1, $CHCl_3$)
7d	CH_3	$CH_2C_6H_5$	$CH(CH_3)_2$	14	+7.5 (*c* 1, $CHCl_3$)
8a	CH_3	$C(CH_3)_3$	CH_3	91[a], 99[b]	+13.7 (*c* 1, $CHCl_3$)
8b	CH_3	$C(CH_3)_3$	C_2H_5	60	+9.3 (*c* 1, $CHCl_3$)
8c	CH_3	$C(CH_3)_3$	C_3H_7	16	+7.3 (*c* 1, $CHCl_3$)
8d	CH_3	$C(CH_3)_3$	$CH(CH_3)_2$	14	+4.3 (*c* 1, $CHCl_3$)
9a	$CH_2C_6H_5$	C_2H_5	CH_3	87	+9.2 (*c* 1, $CHCl_3$)
9b	$CH_2C_6H_5$	C_2H_5	C_2H_5	68	+8.1 (*c* 1, $CHCl_3$)
9c	$CH_2C_6H_5$	C_2H_5	C_3H_7	15	+5.7 (*c* 1, $CHCl_3$)
9d	$CH_2C_6H_5$	C_2H_5	$CH(CH_3)_2$	15	+5.4 (*c* 1, $CHCl_3$)
14a	C_2H_5	$C(CH_3)_3$	C_2H_5	85	+14.7 (*c* 1, $CHCl_3$)
14b	$CH_2C_6H_5$	$C(CH_3)_3$	$CH_2C_6H_5$	61	-5.1 (*c* 1, $CHCl_3$)

[a]NaH (4.8 mmol), MeI (2.85 mmol), DMF, rt, 4 h; [b]NaH (3 mmol), MeI (5 mmol), DMF, rt, 12 h

EXPERIMENTAL

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. ^{1}H spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer using tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on either GCMS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or HRMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). FT-IR spectra (λ_{max} in cm^{-1}) were recorded on a Nicolet spectrometer. 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. All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

Typical procedure for the synthesis of *N*-α-(Carboalkoxy)-*N*-α,*N*-1(τ)-dialkyl-L-histidine methyl esters (7–9). Sodium hydride (60% suspension, 4.8 mmol) was washed with petroleum ether (2 × 5 mL) and dried under vacuum. *N*-α-carboalkoxy-1-alkyl-L-histidine methyl ester [8] (**4**–**6**, 1.89 mmol) in anhydrous DMF (20 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred for another 30 min at ambient temperature, then alkyl iodide (2.85 mmol) was added and the reaction mixture was stirred for another 4 h under N_2. The reaction was quenched by addition of saturated NH_4Cl solution (5 mL) and the solvent removed under reduced pressure. The solid residue was extracted with chloroform (2 × 25 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography eluting with 2% CH_3OH in CH_2Cl_2 to afford *N*-α-(carboalkoxy)-*N*-α,*N*-1(τ)-dialkyl-L-histidine methyl esters **(7–9)** [22].

***N*-α-(Carbobenzyloxy)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester (7a).** Yield: 84%; mp 57-59 °C; ^{1}H nmr ($CDCl_3$): δ 3.25-3.30 (m, 2H), 3.78 (s, 3H), 3.85 (s, 6H), 4.55-4.60 (m, 1H), 5.08 (s, 2H), 7.14 (s, 1H), 7.34 (m, 5H), 9.55 (s, 1H); ESIMS: *m/z* 332 (M+1); $[\alpha]_D^{25}$ +10.5 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found, C, 61.63; H, 6.45; N, 12.77.

***N*-α-(Carbobenzyloxy)-*N*-α-ethyl,*N*-1(τ)-methyl-L-histidine methyl ester (7b).** Yield: 62%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.18 (m, 3H), 3.22-3.30 (m, 2H), 3.84 (s, 3H), 4.11 (m, 5H), 4.49-4.54 (m, 1H), 5.02 (s, 2H), 7.12 (s, 1H), 7.28 (s, 5H), 9.65 (s, 1H); ESIMS: *m/z* 346 (M+1); $[\alpha]_D^{25}$ +8.2 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found, C, 62.78; H, 7.03; N, 11.85.

***N*-α-(Carbobenzyloxy)-*N*-α-propyl,*N*-1(τ)-methyl-L-histidine methyl ester (7c).** Yield: 17%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 0.94 (m, 3H), 1.45 (m, 2H), 3.21-3.29 (m, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 3.99-4.02 (m, 2H), 4.51-4.57 (m, 1H), 5.12 (s, 2H), 7.15 (s, 1H), 7.30 (s, 5H), 9.55 (s, 1H); ESIMS: *m/z* 360 (M+1); $[\alpha]_D^{25}$ +7.9 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found, C, 63.88; H, 7.08; N, 11.47.

***N*-α-(Carbobenzyloxy)-*N*-α-isopropyl,*N*-1(τ)-methyl-L-histidine methyl ester (7d).** Yield: 14%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.48 (d, 6H, *J* = 6.6 Hz), 3.25-3.30 (m, 2H), 3.75 (m, 3H), 3.85 (s, 3H), 4.04-4.06 (m, 1H), 4.50-4.55 (m, 1H), 5.21 (s, 2H), 7.12 (s, 1H), 7.34 (s, 5H), 9.47 (s, 1H); ESIMS: *m/z* 360 (M+1); $[\alpha]_D^{25}$ +7.5 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found, C, 63.81; H, 7.26; N, 11.78.

***N*-α-(*tert*-Butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester (8a).** Yield: 91%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.41 (s, 9H), 3.24-3.27 (m, 2H), 3.81 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 4.51-4.60 (m, 1H), 7.32 (s, 1H), 9.70 (s, 1H); ESIMS: *m/z* 298 (M+1); $[\alpha]_D^{25}$ +13.7 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{14}H_{23}N_3O_4$: C, 56.55; H, 7.80; N, 14.13. Found, C, 56.51; H, 7.69; N, 14.34.

***N*-α-(*tert*-Butoxycarbonyl)-*N*-α-ethyl,*N*-1(τ)-methyl-L-histidine methyl ester (8b).** Yield: 60%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.40 (s, 9H), 1.61 (t, 3H, *J* = 7.3 Hz), 3.20-3.26 (m, 2H), 3.79 (s, 3H), 4.02 (s, 3H), 4.24 (q, 2H, *J* = 7.2 Hz), 4.50-4.58 (m, 1H), 7.26 (s, 1H, 5-H), 9.89 (s, 1H); ESIMS: *m/z* 312

(M+1); $[\alpha]_D^{25}$ +9.3 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{15}H_{25}N_3O_4$: C, 57.86; H, 8.09; N, 13.49. Found, C, 57.93; H, 8.34; N, 13.58.

***N*-α-(*tert*-Butoxycarbonyl)-*N*-α-propyl,*N*-1(τ)-methyl-L-histidine methyl ester (8c).** Yield: 16%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.00 (m, 3H), 1.40 (s, 9H), 1.60 (m, 2H), 3.22-3.26 (m, 2H), 3.79 (s, 3H), 3.89-3.92 (m, 2H), 4.05 (s, 3H), 4.53-4.60 (m, 1H), 7.30 (s, 1H), 9.84 (s, 1H); ESIMS: *m/z* 326 (M+1); $[\alpha]_D^{25}$ +7.3 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found, C, 58.78; H, 8.22; N, 13.25.

***N*-α-(*tert*-Butoxycarbonyl)-*N*-α-isopropyl,*N*-1(τ)-methyl-L-histidine methyl ester (8d).** Yield: 14%; semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.43 (s, 9H), 1.52 (d, 6H, *J* = 6.7 Hz), 3.20-3.27 (m, 2H), 3.83 (s, 3H), 3.90-3.94 (m, 1H), 4.05 (s, 3H), 4.55-4.61 (m, 1H), 7.28 (s, 1H), 9.80 (s, 1H); ESIMS: *m/z* 326 (M+1); $[\alpha]_D^{25}$ +4.3 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found, C, 59.34; H, 8.64; N, 12.67.

***N*-α-(Ethoxycarbonyl)-*N*-α-methyl,*N*-1(τ)-benzyl-L-histidine methyl ester (9a).** Yield: 87%; mp 68-69 °C; ^{1}H nmr ($CDCl_3$): δ 1.16 (m, 3H), 3.25-3.30 (m, 2H), 3.71 (s, 3H), 3.92-3.97 (m, 5H), 4.55-4.60 (m, 1H), 5.47 (s, 2H), 7.32-7.36 (m, 5H), 7.14 (s, 1H); 9.81 (s, 1H); ESIMS: *m/z* 332 (M+1); $[\alpha]_D^{25}$ +9.2 (*c* = 1, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.17. Found, C, 62.68; H, 6.84; N, 12.06.

***N*-α-(Ethoxycarbonyl)-*N*-α-ethyl,*N*-1(τ)-benzyl-L-histidine methyl ester (9b).** Yield: 68%; mp 62-63 °C; ^{1}H nmr ($CDCl_3$): δ 1.06-1.18 (m, 6H), 3.18-3.24 (m, 2H), 3.63 (s, 3H), 3.91-3.94 (m, 2H), 4.16 (q, 2H, *J* = 7.2 Hz), 4.45-4.58 (m, 1H), 5.45 (s, 2H), 7.29-7.32 (m, 5H), 7.45 (s, 1H), 9.91 (s, 1H); ESIMS: *m/z* 360 (M+1); $[\alpha]_D^{25}$ +8.1 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found, C, 63.63; H, 7.09; N, 11.78.

***N*-α-(Ethoxycarbonyl)-*N*-α-propyl,*N*-1(τ)-benzyl-L-histidine methyl ester (9c).** Yield: 15%, semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.10-1.20 (m, 6H), 1.89-1.94 (m, 2H), 3.20-3.25 (m, 2H), 3.70 (s, 3H), 3.91-3.94 (m, 2H), 4.20-4.24 (m, 2H), 4.47-4.53 (m, 1H), 5.41 (s, 2H), 7.24-7.27 (m, 5H), 7.40 (s, 1H), 9.87 (s, 1H); ESIMS: *m/z* 374 (M+1); $[\alpha]_D^{25}$ +5.7 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.27; N, 11.25. Found, C, 64.47; H, 7.15; N, 11.08.

***N*-α-(Ethoxycarbonyl)-*N*-α-isopropyl,*N*-1(τ)-benzyl-L-histidine methyl ester (9d).** Yield: 15%, semi-solid; ^{1}H nmr ($CDCl_3$): δ 1.14-1.13 (m, 3H), 1.60 (d, 6H, *J* = 6.6 Hz), 3.21-3.24 (m, 2H), 3.72 (s, 3H), 3.90-3.92 (m, 2H), 4.20-4.24 (m, 1H), 4.43-4.48 (m, 1H), 5.46 (s, 2H), 7.21-7.24 (m, 5H), 7.34 (s, 1H), 9.80 (s, 1H); ESIMS: *m/z* 374 (M+1); $[\alpha]_D^{25}$ +5.4 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.27; N, 11.25. Found, C, 64.17; H, 7.14; N, 11.16.

Typical procedure for the synthesis of *N*-α,*N*-1(τ)-dialkyl-L-histidine hydrochloride (10–11). A solution of **7a** or **9a** (1 mmol) in 6 *N* HCl (15 mL), was heated at reflux for 8 h. The hydrochloride salts **10–11** of the *N*-α,*N*-1(τ)-dialkyl-L-histidines were obtained directly by evaporation of the acidic hydrolysis solution.

***N*-α,*N*-1(τ)-Dimethyl-L-histidine hydrochloride (10).** Yield: 98%; mp 164-166 °C (dec); ^{1}H nmr (CD_3OD): δ 3.32-3.50 (m, 2H), 3.91 (s, 3H), 3.93 (s, 3H), 4.40-4.50 (m, 1H), 4.52 (brs, 1H), 7.59 (s, 1H), 8.95 (s, 1H); ESIMS: *m/z* 184 (M+1); $[\alpha]^D_{25}$ –10.2 (*c* 1, H_2O). *Anal.* Calcd. for $C_8H_{14}ClN_3O_2$: C, 43.74; H, 6.42; N, 19.13. Found, C, 43.54; H, 6.73; N, 19.35.

***N*-α-Benzyl,*N*-1(τ)-methyl-L-histidine hydrochloride (11).** Yield: 94%, mp 178-180 °C (dec); ^{1}H nmr (CD_3OD) δ 3.38-3.41 (m, 2H), 3.92 (s, 3H), 4.45-4.48 (m, 1H), 5.0 (brs, 1H), 5.44 (s, 2H), 7.43-7.48 (m, 5H), 7.66 (s, 1H), 9.11 (s, 1H); ESIMS: *m/z* 260 (M+1); $[\alpha]^D_{25}$ –12.7 (*c* 1, H_2O). *Anal.* Calcd. for $C_{14}H_{18}ClN_3O_2$: C, 56.85; H, 6.13; N, 14.21. Found, C, 56.64; H, 6.47; N, 14.59.

Synthesis of *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine (12). *N*-α-(*tert*-Butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester (**8a**, 1.68 mmol) was dissolved in methanol (30 mL). A solution of $LiOH.H_2O$ (2.52 mmol) in water (5 mL) was added, and reaction mixture was stirred at ambient temperature for 30 min. Solvent was removed under reduced pressure and crude product was purified by silica gel (230-400 mesh) column chromatography eluting with 10% CH_3OH in CH_2Cl_2 to afford **12**. Yield: 91%; mp 122-124 °C; ^{1}H nmr (CD_3OD): δ 1.41 (s, 9H), 2.83-3.04 (m, 2H), 3.69 (s, 3H), 3.71 (s, 3H), 4.30-4.38 (m, 1H), 6.89 (s, 1H), 7.60 (s, 1H); ESIMS *m/z* 284 (M+1); $[\alpha]^D_{25}$ +14.2 (*c* 1, CH_3OH). *Anal.* Calcd. for $C_{13}H_{21}N_3O_4$: C, 55.11; H, 7.47; N, 14.83. Found, C, 55.02; H, 7.25; N, 14.74.

Typical procedure for the synthesis of *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester (8a) and *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-diethyl-L-histidine methyl ester (14a). Sodium hydride (60% suspension, 3 mmol) was washed with petroleum ether (2 × 5 mL) and dried under vacuum. *N*-α-(*tert*-butoxycarbonyl)-L-histidine methyl ester (**13**, 1 mmol) in anhydrous DMF (20 mL) was added under a nitrogen atmosphere. The reaction mixture was stirred for another 30 min at ambient temperature. Methyl iodide or ethyl iodide (5 mmol) was added and the reaction mixture was stirred for another 12 h under N_2 at ambient temperature. The reaction was quenched by addition of saturated NH_4Cl solution (5 mL) and the solvent removed under reduced pressure. The solid residue was extracted with chloroform (2 × 15 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography eluting with 2-4% CH_3OH in CH_2Cl_2 to afford *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dimethyl-L-histidine methyl ester (**8a**) and *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-diethyl-L-histidine methyl ester (**14a**).

***N*-α-(*tert*-Butoxycarbonyl)-*N*-α,*N*-1(τ)-diethyl-L-histidine methyl ester (14a).** Yield: 85%, oil; ^{1}H nmr ($CDCl_3$): δ 1.41 (s, 9H), 1.60-1.65 (m, 6H), 3.09-3.12 (m, 2H), 3.68 (s, 3H), 4.28-4.32 (m, 4H), 4.53-4.57 (m, 1H), 7.24 (s, 1H), 9.67 (s, 1H); ESIMS: *m/z* 326 (M+1); $[\alpha]_D^{25}$ +14.7 (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{16}H_{27}N_3O_4$ (325.4): C, 59.06; H, 8.36; N, 12.91. Found, C, 59.31; H, 8.39; N, 13.06.

Synthesis of *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dibenzyl-L-histidine methyl ester (14b). Sodium hydride (60% suspension, 1.11 mmol) was washed with petroleum ether (2 × 5 mL) and dried under vacuum. *N*-α-(*tert*-butoxycarbonyl)-L-histidine methyl ester (**13**, 0.37 mmol) dissolved in DMF (5 mL) was added and reaction mixture stirred for 2 h at ambient temperature under N_2. Benzyl bromide (1.85 mmol) was then added and reaction mixture stirred for 10 h at 80 ºC. The reaction was quenched by addition of saturated NH_4Cl solution (5 mL) and the solvent removed under reduced pressure. The solid residue was extracted with chloroform (2 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel (230–400 mesh) column chromatography eluting with 4% CH_3OH in CH_2Cl_2 to afford *N*-α-(*tert*-butoxycarbonyl)-*N*-α,*N*-1(τ)-dibenzyl-L-histidine methyl

ester **(14b)**. Yield: 61%, oil; ^{1}H nmr ($CDCl_3$): δ 1.34 (s, 9H), 3.00-3.04 (m, 2H), 3.39 (s, 3H), 4.53-4.58 (m,1H), 5.55-5.57 (m, 4H), 7.33-7.40 (m, 10H), 7.48 (s, 1H), 9.79 (s, 1H); ESIMS: *m/z* 450 (M+1); $[\alpha]_D^{25}$ -5.1 (*c* 1, $CHCl_3$). *Anal*. Calcd. for $C_{26}H_{31}N_3O_4$ (449.5): C, 69.47; H, 6.95; N, 9.35. Found, C, 69.12; H, 7.24; N, 8.97.

Typical procedure for the synthesis of *N*-α,*N*-1(τ)-diethyl-L-histidine hydrochloride (15a) and *N*-α,*N*-1(τ)-dibenzyl-L-histidine hydrochloride (15b). These compounds were synthesized using procedure described above for compounds **10**-**11**.

***N*-α,*N*-1(τ)-Diethyl-L-histidine hydrochloride (15a).** Yield: 90%, mp 178-180 °C (dec); ^{1}H nmr (CD_3OD): δ 0.96 (m, 3H), 1.21 (m, 3H), 3.35-3.41 (m, 6H), 4.22-4.25 (m, 1H), 4.90 (brs, 1H), 7.62 (s, 1H), 8.94 (s, 1H); ESIMS: *m/z* 212 (M+1); $[\alpha]^D_{25}$ −14.6 (*c* 1, H_2O). *Anal*. Calcd. for $C_{10}H_{18}ClN_3O_2$: C, 48.48; H, 7.32; N, 16.96. Found, C, 48.70; H, 7.51; N, 17.07.

***N*-α,*N*-1(τ)-Dibenzyl-L-histidine hydrochloride (15b).** Yield: 92%, mp 191-193 °C (dec); ^{1}H nmr (CD_3OD): δ 3.31-3.37 (m, 2H), 4.40-4.45 (m, 1H), 4.95 (brs, 1H), 5.21-5.25 (m, 4H), 7.25-7.30 (m, 10H), 7.65 (s, 1H), 8.97 (s, 1H); ESIMS: *m/z* 336 (M+1); $[\alpha]^D_{25}$ −10.1 (*c* 1, H_2O). *Anal*. Calcd. for $C_{20}H_{22}ClN_3O_2$: C, 64.60; H, 5.96; N, 11.30. Found, C, 64.94; H, 5.77; N, 11.58.

Acknowledgement. Navneet Kaur and Vikramdeep Monga thank the University Grants Commission (UGC), India, and the Council of Scientific and Industrial Research (CSIR, Grant No. 01(1861)/03/EMR-II), India, respectively for the award of Senior Research Fellowship.

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