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Facile one-step synthesis of *N*-α-Boc-1-alkyl-L-histidines

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Abstract—*N*-α-Boc-L-Histidine upon direct τ(N-1) ring alkylation with various alkyl halides in the presence of sodium hydride in DMF or CH_3CN easily afforded *N*-α-Boc-1-alkyl-L-histidines **2a–f**. The reaction works equally well in either DMF or CH_3CN as solvent, however, CH_3CN is preferred due to ease of reaction work-up.

Due to their structural diversity and versatility, synthetic nonproteinogenic amino acids are increasingly becoming very important substrates in modern drug design, synthesis and discovery research. These chiral building blocks are highly useful as scaffolds in constructing combinatorial small molecule and peptide libraries. In particular, synthetic or modified α-amino acids play a significant role in the area of peptide research and are extensively incorporated into biologically active peptides to restrict their conformational flexibility, enhance proteolytic stability, increase selectivity and improve pharmacodynamics and bioavailability properties.[1–3] The incorporation of modified α-amino acids into bioactive peptides is also known to provide useful information regarding size and steric requirements for receptor-binding interactions of these substrates at the binding pocket of the receptor.[4–6]

Our interest in histidine and histamine derivatives as polypeptide components and novel antimalarial agents resulted in successful syntheses of various ring-substituted bioimidazoles.[7–13] Recently, our requirement of $N(1)^{\tau}$-alkyl-L-histidines as components of thyrotropin-releasing hormone (TRH) peptide analogues created a need for various *N*-α-Boc-1-alkyl-L-histidines on a preparative scale suitable for incorporation into the target peptides by solid phase synthesis. Previously, we have reported the synthesis of $N(1)^{\tau}$-alkyl-L-histidines starting from L-histidine methyl ester via (7*S*)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-*c*]pyrimidine in four steps,[7] which upon reaction with di-*tert*-butyl dicarbonate using standard α-amino group protection protocol[14] could provide *N*-α-Boc-1-alkyl-L-histidines. However, preparation of the *N*-α-Boc-1-alkyl-L-histidines requires five overall steps and involves the expensive reagent 1,1′-carbonyl-diimidazole, thereby rendering this approach uninviting. Thus, we searched for a short synthetic route that would allow easy access to these important scaffolds, and herein, we report a facile and direct one-step synthesis of *N*-α-Boc-1-alkyl-L-histidines **2a–f**.

Specific alkylation at the τ(N-1) position of the imidazole ring in histidine generally requires protection at the π(N-3) position as direct ring alkylation of histidine almost always results in a mixture of τ(N-1) and π(N-3) derivatives. Although the τ derivative is the major product, it is rarely formed exclusively, and only a few classes of reagents, the halonitrobenzenes,[15] triarylmethyl halides[16] and *tert*-butylbromoacetate[17] routinely appear to give exclusive τ(N-1) products. It has been reported that *N*-α-trityl-L-histidine, upon reaction with iodomethane and sodium hydride (NaH) in DMF/THF at −10 °C, led to the formation of *N*-α-trityl-1-methyl-L-histidine (major product) along with *N*-α-trityl-3-methyl-L-histidine (minor product).[18] On the other hand, benzylation of the imidazole ring in unprotected L-histidine with benzyl chloride in the presence of sodium metal produced 1-benzyl-L-histidine exclusively[19].

We observed that *N*-α-Boc-L-histidine undergoes selective deprotonation at low temperature in DMF with

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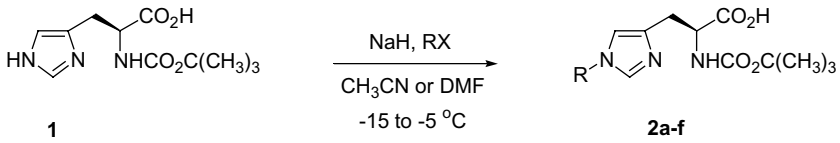

1 2a-f

Scheme 1.

NaH, which upon reaction with various alkyl halides such as, iodomethane, iodoethane, 1-bromopropane, 2-bromopropane, 2-bromobutane and benzyl bromide produces exclusively τ(N-1) alkylated *N*-α-Boc-L-histidine derivatives.[20,21] Thus, reaction of *N*-α-Boc-L-histidine with NaH at −15 °C for 30 min in anhydrous DMF, followed by addition of the appropriate commercially available alkyl halides at −5 °C and stirring 4 h readily produced *N*-α-(*tert*-butoxycarbonyl)-1-alkyl-L-histidines **2a**–**f** (Scheme 1). All the *N*-α-(*tert*-butoxycarbonyl)-1-alkyl-L-histidines **2a**–**f** were obtained in moderate to satisfactory yields, however, we faced problems relating to the stability of the products during work-up of the reaction, presumably because of the elevated temperature required to remove DMF. We then attempted the alkylation reaction in anhydrous CH_3CN as solvent and observed identical results, and therefore CH_3CN is preferred due to ease of reaction work-up.

The reaction allows easy entry to histidine derivatives with various primary alkyl groups (methyl, ethyl, *n*-propyl), secondary alkyl groups (*i*-propyl, *sec*-butyl) and a benzyl group and can also be conveniently adapted to include many other alkyl groups. Unfortunately, all attempts towards incorporation of an allyl or a cyclopropyl group resulted in the recovery of starting material along with some unidentified higher molecular weight products (Table 1).

To summarize, we have successfully established a convenient and cost-effective one-step synthetic procedure for the preparation of several previously inaccessible *N*-α-Boc-1-alkyl-L-histidines. Attempts to further extend this methodology to include allyl and cyclopropyl groups failed. However, it can be safely concluded that the method discussed provides exclusive and easy entry to a diverse range of primary and secondary alkyl groups substituted at the N-1 position of the imidazole ring of *N*-α-Boc-L-histidine.

Typical procedure for the synthesis of N-α-(tert-butoxycarbonyl)-1-alkyl-L-histidines **2a**–**f**: Sodium hydride (60% suspension, 11.7 mmol) was placed in a two-necked flask, washed with anhydrous benzene (2 × 10 mL) and dried under vacuum. *N*-α-Boc-L-histidine (**1**, 3.9 mmol) in DMF or CH_3CN (20 mL) was added under a nitrogen atmosphere at −15 °C. The reaction mixture was stirred for another 30 min at −15 °C, then alkyl halide (7.8 mmol) was added. The temperature of the reaction was raised to −5 °C, and the reaction mixture was stirred for another 4 h under N_2. The reaction was quenched by addition of methanol (5 mL) and the solvent removed under reduced pressure. The solid residue was extracted with chloroform (4 × 50 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 13% CH_3OH in CH_2Cl_2 to afford *N*-α-(*tert*-butoxycarbonyl)-1-alkyl-L-histidines **2a**–**f**.[22,23]

Spectral data of N-α-(tert-butoxycarbonyl)-1-methyl-L-histidine **2a**: Yield: 94%; ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 3.02 (m, 2H), 3.64 (s, 3H), 4.06 (m, 1H), 6.73 (s, 1H), 7.40 (s, 1H); APCI MS *m*/*z* 270 (M+1); analysis for $C_{12}H_{19}N_3O_4$ (269.3), calcd, C, 53.52; H, 7.11; N, 15.60; found, C, 53.89; H, 6.91; N, 15.87; $[\alpha]_D^{25}$ +17.1 (*c* 1, CH_3OH).

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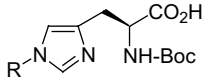
Table 1. Physical data of *N*-α-Boc-1-alkyl-L-histidines



Product	R	Alkyl halide (RX)	Yield (%)	$[\alpha]_D^{25}$
2a	CH_3	CH_3I	94	+17.1 (*c* 1, CH_3OH)
2b	C_2H_5	C_2H_5I	80	+15.4 (*c* 1, CH_3OH)
2c	C_3H_7	C_3H_7Br	75	+13.5 (*c* 1, CH_3OH)
2d	$CH(CH_3)_2$	$(CH_3)_2CHBr$	71	+17.6 (*c* 1, CH_3OH)
2e	$CH(CH_3)(C_2H_5)$	$C_2H_5CH(Br)CH_3$	33	—
2f	$CH_2C_6H_5$	$C_6H_5CH_2Br$	25	+19.6 (*c* 1, CH_3OH)
2g	$CH_2CH{=}CH_2$[a]	$H_2C{=}CHCH_2Br$	—	—
2h	*c*-C_3H_5[a]	*c*-C_3H_5Br	—	—

[a] No reaction.

References and notes

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20. The observation of exclusive τ(N-1) alkylation of *N*-α-Boc-L-histidine was authenticated as follows: Histidine derivatives **2a**–**f** were subjected to acidic hydrolysis with CF_3CO_2H (10% solution in DCM) for 30 min. A solution of 1-alkyl-L-histidine trifluoroacetate salt in water was applied to an ion-exchange column (Dowex 50×2–200, H^+ form). The column was eluted with water until the eluent was neutral to pH paper. The modified amino acid was then eluted with 25% NH_4OH solution. Evaporation of the solvent provided free 1-alkyl-L-histidines, and their spectroscopic data and physical properties were found to be identical upon comparison to earlier reported data. Jain, R.; Cohen, L. A. *Tetrahedron* **1996**, *52*, 5363–5370.
21. 1-Propyl-L-histidine was synthesized from *N*-α-(*tert*-butoxycarbonyl)-1-propyl-L-histidine **2c** using the procedure reported in Ref. 20. Spectral data: Yield: 95%; ^{1}H NMR (D_2O): δ 0.91 (t, 3H, $J = 7.2$ Hz), 1.90 (m, 2H), 3.03 (m, 2H), 3.91 (t, 2H, $J = 7.1$ Hz), 4.04 (m, 1H), 6.92 (s, 1H), 7.66 (s, 1H); APCI MS *m/z* 198 (M+1); analysis for $C_9H_{15}N_3O_2$ (197.2), calcd, C, 54.81; H, 7.67; N, 21.30; found, C, 54.97; H, 7.51; N, 21.53; $[\alpha]_D^{25}$ −30.1 (*c* 1, H_2O).
22. *Spectral data of N-α-(tert-butoxycarbonyl)-1-propyl-L-histidine* **2c**. Yield: 75%; ^{1}H NMR (CD_3OD): δ 0.86 (t, 3H, $J = 7.3$ Hz), 1.39 (s, 9H), 1.78 (m, 2H), 3.07 (m, 2H), 3.91 (t, 2H, $J = 7.0$ Hz), 4.10 (m, 1H), 6.90 (s, 1H), 7.98 (s, 1H); APCI MS *m/z* 298 (M+1); analysis for $C_{14}H_{23}N_3O_4$ (297.4), calcd, C, 56.55; H, 7.80; N, 14.13; found, C, 56.34; H, 7.99; N, 14.51; $[\alpha]_D^{25}$ +13.5 (*c* 1, CH_3OH).
23. *Spectral data of N-α-(tert-butoxycarbonyl)-1-isopropyl-L-histidine* **2d**. Yield: 71%; ^{1}H NMR (CD_3OD): δ 1.43 (s, 9H), 1.58 (d, 6H, $J = 6.6$ Hz), 2.96 (m, 2H), 4.06 (m, 1H), 4.10 (m, 1H), 6.80 (s, 1H), 8.02 (s, 1H); APCI MS *m/z* 298 (M+1); analysis for $C_{14}H_{23}N_3O_4$ (297.4), calcd, C, 56.55; H, 7.80; N, 14.13; found, C, 56.87; H, 7.65; N, 13.88; $[\alpha]_D^{25}$ +17.6 (*c* 1, CH_3OH).