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(*S*)-Histidine: the ideal precursor for a novel family of chiral aminoacid and peptidic ionic liquids

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Abstract—(*S*)-Histidine is shown to be a powerful chiral precursor for the construction of a new series of imidazolium-containing chiral ionic liquids, in which the chiral bifunctional unit of the aminoacid remains unchanged. These ionic materials can be used as building blocks for the synthesis of peptidic ionic liquids.

The search for new solvents and materials based on chiral ionic liquids is a topic of increasing importance, since numerous applications including asymmetric synthesis, chiral chromatography, stereoselective polymerizations, and NMR chiral discrimination have been recently described in the literature.[1] This research topic also constitutes a new creative area for organic chemists since 'tailor made' structures can be imagined and synthesized for various purposes, such as chiral solvents, task-specific ionic liquids, and immobilized catalyst. As an example, some of us recently described a new series of compounds, which exhibited both properties of ionic liquids and of chiral liquid crystals.[2]

For the construction of chiral ionic liquids, one of the most prominent series of starting material taken from the chiral pool is that of α-aminoacids, which are readily available at low cost and offer interesting molecular diversity from which could be built a large variety of structures. Various chiral ionic liquids were previously built starting from α-aminoacids.[3–9] Although of powerful synthetic utility, none of the strategies used led to chiral ionic liquids in which the aminoacid bifunctional unit remains intact, the aminoacid being either transformed or used as an ionic part of the salt.

In connection with our insights about peptide synthesis in ionic liquids,[10] we envisioned (*S*)-histidine, a commercially available natural aminoacid, as a key chiral starting material for the elaboration of dissymmetric imidazolium moieties by direct modification of the side chain, thus leaving free the aminoacid function of the obtained chiral ionic liquids (Fig. 1).[4,11] Thus, usual aminoacid chemistry can be performed on the functionalized ionic liquid. During the course of this study, Chan et al. described the use of an achiral imidazolium salt as a support for peptide synthesis.[12]

In order to selectively alkylate both N-positions of the imidazole ring while leaving the primary amine function untouched, we chose to rely on a reported procedure, which has been previously used to alkylate either the N-1[13] or the N-3[14] (via the temporary protection of N-1) position of histidine. As reported by Cohen,[13] treatment of the histidine methyl ester dihydrochloride with carbonyldiimidazole in DMF afforded the cyclic urea **1** as a white crystalline solid in a good yield. However, the reported procedure requires quite a large amount of DMF that has to be evaporated off at the end of

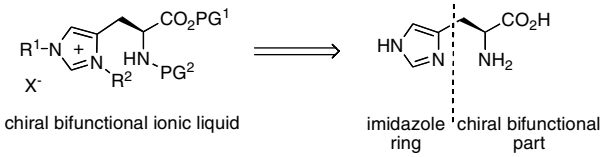

Figure 1. Chiral ionic liquids starting from (*S*)-histidine.

Keywords: Histidine; Aminoacid; Peptide; Chiral ionic liquid; Imidazolium.
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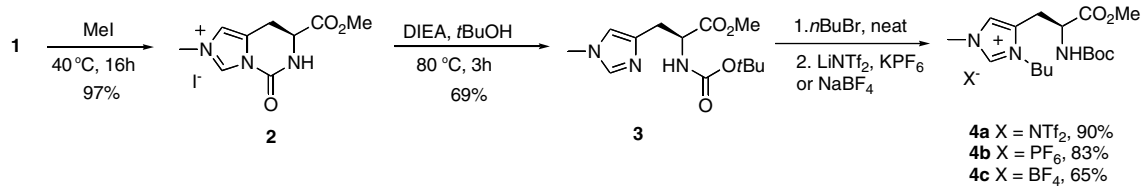
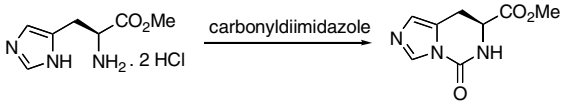


Scheme 1. Synthesis of bis-protected histidinium salts.

the reaction. As the only byproduct of the reaction is imidazole hydrochloride, which can (despite its rather high melting point of 158–161 °C) be considered as the prototype of lower melting imidazolium salts, we reasoned that the reaction could be run without solvent by mixing the two solid compounds with heating, relying on the in situ generated salt to obtain a homogeneous reaction mixture. We were delighted to see that, upon heating a mixture of carbonyldiimidazole and histidine methyl ester dihydrochloride with vigorous mechanical stirring, a viscous liquid was obtained in a few minutes at temperatures as low as 80 °C (Eq. 1). After hydrolysis and extraction with dichloromethane, the expected cyclic urea **1** was obtained in good yield and excellent chemical purity after simple washing with diethylether.[15] It should be noted that, although the reaction temperature is much lower than any of the reactant or product's melting point, the crude reaction mixture is a homogeneous viscous liquid.



(1)

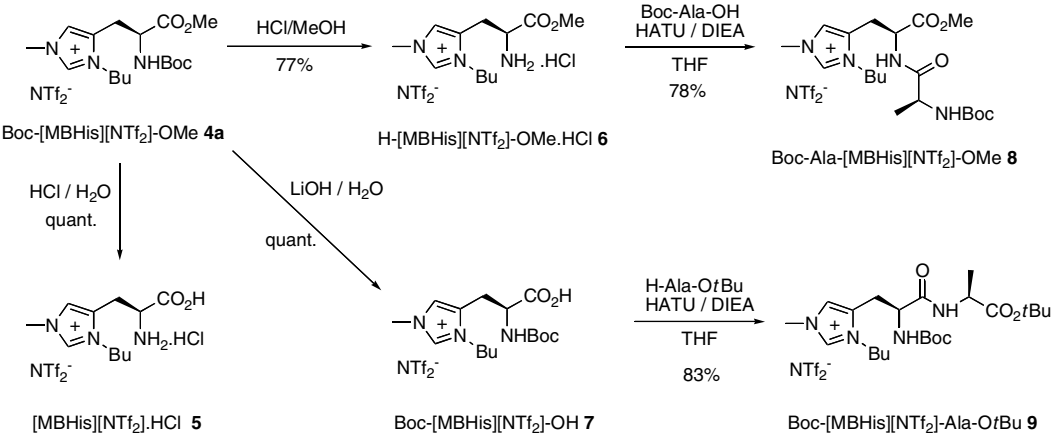
DMF, 70 °C, 3h	74%
no solvent, 80 °C, 30 min	82%
no solvent, 100 °C, 10 min	77%

Alkylation of **1** with methyl iodide in acetonitrile proceeded smoothly to give the corresponding salt **2** in high yield as a crystalline, high melting solid. The cyclic urea **2** was then opened by *tert*-butanol in the presence of diisopropylethylamine, to give the Boc-protected N(1)-alkylated histidine methyl ester **3**.[13,16] Alkylation of **3** proceeded smoothly with *n*-iodobutane in acetonitrile or, more conveniently, with neat *n*-bromobutane to give the desired new chiral imidazolium salts. This strategy allows inversion of the substitution pattern of the imidazolium ring by simply inverting the alkylation steps.

The resulting hygroscopic halide salts were immediately engaged in an anion exchange reaction with lithium bistriflimide,[17] potassium hexafluorophosphate, or sodium tetrafluoroborate (Scheme 1). The resulting liquid[18] salts could be purified by flash column chromatography on silica gel.

As these new species pertain to both aminoacid and ionic liquid chemistry, we propose a naming system based on aminoacid and peptide nomenclature, where the ionic histidine-based imidazolium is represented as an ionic liquid, that is with both anion and cation in brackets. The imidazolium substituents (namely methyl and butyl) have to be represented by their initial letter (the N-1 substituent before the N-3 substituent) in the cationic part. For instance, ionic liquid **4a** will be named Boc-[MBHis][NTf_2]-OMe.

The most interesting term of this series, namely **4a** (X = NTf_2) was conveniently transformed into various ionic structures by means of typical methods in aminoacid chemistry (Scheme 2). Complete deprotection by aqueous HCl quantitatively afforded the hydrosoluble aminoacid hydrochloride **5**. Selective deprotection was performed either by hydrolysis of **4a** with HCl in anhy-



Scheme 2. Access to (*S*)-histidinium [MBHis][X] derivatives.

drous methanol affording the aminoester hydrochloride **6** in 77% yield, or by saponification using lithium hydroxide, quantitatively affording the N-protected aminoacid **7**.

In order to assess the ability of the novel imidazolium aminoacid derivatives to undergo peptidic coupling at either N- or C-terminal position, monoprotected aminoacids **6** and **7** were reacted with *N*-Boc-alanine (respectively, alanine *tert*-butylester) using HATU as the coupling agent and DIEA as a base, affording the desired dipeptide **8**[19] (respectively, **9**) in good yield (Scheme 2). Only one diastereoisomer of each dipeptide was obtained, confirming that no racemization occurred during the series of synthetic steps.

Worthy of note is that peptide coupling under standard conditions leads to the desired targets in excellent yields after purification, although starting from unprecedented ionic structures.

In this letter, we describe a handy access to a novel family of chiral ionic liquids starting from an easily available aminoacid, namely (*S*)-Histidine. The key target [MBHis][NTf_2] is obtained either unprotected, mono N- or O-protected or fully protected on both functions. Peptide coupling is shown to be as efficient on this new aminoacid as in classical examples and occurs without racemization. Further studies are currently underway to complete this new family of chiral ionic liquids, to establish their structure/physicochemical data relationship, and to examine various organocatalyzed enantioselective reactions by means of these new chiral tools.

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15. Solid histidine methyl ester dihydrochloride (1.21 g, 5 mmol) and carbonyldiimidazole (1.05 g, 6.5 mmol) were heated to 80 °C with vigorous mechanical stirring under a flow of nitrogen. After 30 min, the viscous, slightly yellowish liquid obtained was hydrolyzed with 5 mL H_2O, and the aqueous phase was extracted with 5×20 mL of CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum until precipitation of a white solid. Diethyl ether (200 mL) was then added, and the product was filtered on a sintered glass Büchner, washed with ether and dried to give analytically pure **1** as a white crystalline solid (802 mg, 82%).
16. Enantiomeric purity of **3** was ascertained by chiral HPLC (chiralcel AD-H, hexane/EtOH 1/1).
17. Analytical data for Boc-[MBHis][NTf_2]-OMe **4a**: mp 46.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (3H, t, $J = 7$ Hz), 1.30–1.50 (2H, m), 1.41 (9H, s), 1.76–1.87 (2H, m), 3.10 (1H, dd, $J = 8$ Hz, $J = 16$ Hz), 3.25 (1H, dd, $J = 5$ Hz, $J = 16$ Hz), 3.80 (3H, s), 3.88 (3H, s), 4.0–4.2 (2H, m), 4.51–4.56 (1H, m), 5.45–5.48 (1H, m), 7.10 (1H, s), 8.67 (1H, s). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.4, 19.6, 26.5, 28.2, 32.0, 36.3, 47.3, 52.4, 53.2, 80.9, 119.9 (q, $^1J_{CF} = 321$ Hz), 121.8, 131.5, 136.0, 155.7, 170.7. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ −79.4. $[\alpha]_D^{20}$ +7.7 (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}F_6N_4O_8S_2$: C, 36.77; H, 4.87; N, 9.03; S, 10.33. Found: C, 36.86; H, 4.34; N, 8.98; S, 10.41. MS (ESI): *m*/*z* 340 (M^+, 32), 284 (100), 240 (4).
18. Although these salts present a melting point (determined by DSC) above room temperature, ionic liquids are easily found in supercooled state.
19. Synthesis of Boc-Ala-[MBHis][NTf_2]-OMe **8**: A round bottomed flask was charged with 141 mg of **6** (0.25 mmol), 48 mg of Boc-(*S*)-Ala-OH (0.25 mmol, 1 equiv), and 97 mg of HATU (0.25 mmol, 1 equiv), and flushed with argon. THF (10 mL) was then added and the mixture was stirred at 0 °C for 20 min. After addition of 70 μL of DIEA (0.76 mmol, 3 equiv), the mixture was allowed to warm up to room temperature. After 18 h, THF was evaporated off and the residue was taken up in 10 mL of CH_2Cl_2, washed with 8 mL of 1 M $NaHCO_3$ solution, 2×8 mL of 10% aqueous citric acid solution, and 8 mL of water. The organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by chromatography on silica gel (CH_2Cl_2/acetone: 8/2) led to pure **8** as a colorless viscous oil (136 mg, 78%). $[\alpha]_D^{20}$ −15 (*c* 1.44, acetone). ^{1}H NMR (CD_3CN, 300 MHz) δ 0.95 (3H, t, $J = 7.3$ Hz), 1.22 (3H, d, $J = 7.2$ Hz), 1.30–1.45 (2H, m), 1.39 (9H, s), 1.70–1.85 (2H, m), 3.04 (1H, dd, $J = 9.3$ Hz,

$J = 16.2$ Hz), 3.21 (1H, dd, $J = 4.9$ Hz, $J = 16.2$ Hz), 3.71 (3H, s), 3.77 (3H, s), 3.94 (1H, m), 4.06 (2H, t, $J = 7.5$ Hz), 4.65–4.75 (1H, m), 5.57 (1H, d, $J = 4.9$ Hz), 7.08 (1H, d, $J = 7.9$ Hz), 7.18 (1H, s), 7.77 (1H, s). ^{19}F NMR (CD_3CN, 282.4 MHz) δ −80.66. ^{13}C NMR (CD_3CN, 75.5 MHz) δ 13.6, 17.9, 20.0, 26.1, 28.4, 32.2, 36.8, 47.6, 51.1, 53.3, 55.9, 79.9, 120.8 (q, $J_{C-F} = 321$ Hz), 122.7, 131.9, 136.3, 156.4, 171.4, 174.3.