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Synthesis and structural study of 6-amino-1,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones

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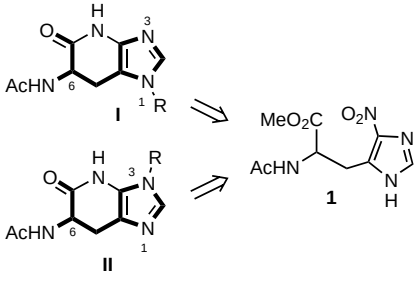
Abstract—6-Amino-1,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones are new heterocyclic scaffolds which can be used as conformationally restricted His analogues and as modified purines. We have prepared imidazopiperidones **7** using *N*-α-acetyl-4-nitrohistidine methyl ester as the starting material. NMR studies and molecular modelling calculations on a surrogate of the His-Gly dipeptide **10** are also commented. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have continued our studies on valerolactam-derived conformationally restrained pseudodipeptides,[1] by focusing on the synthesis of histidine derivatives. The main biological roles of histidine depend on its capacity to act as an amphoteric species through the tautomeric equilibrium of the imidazole ring,[2] as exemplified by the cleavage of peptides and proteins by serine[3] and cysteine proteases.[4] In addition, histidine is an important aminoacid at the active site of many enzymes, and often appears to be essential for the recognition of peptide hormones by their receptors.[5]

By diminishing the conformational space of the histidine side chain, and by fixing the orientation of the tautomeric form within the original structures, we intend to determine the active conformation of several histidine-containing drugs or peptides.



Scheme 1.

Accordingly, we designed compound **I** (Scheme 1), in which the imidazole ring is fused to the piperidone, and the χ_i dihedral angles of histidine are practically immobilized. Compound **I** can also be regarded as a modified purine,[6] and as such would enhance the scope for application of this nucleus.

Our first goal was to establish a convenient way to prepare the heterocyclic system **I**, and to explore the possibility of obtaining its regioisomer **II**. The second aim was to study the reactivity of compound **I**, and to prepare compounds **9a** and **9c** as models for studying the system as a constrained analogue of the His-Gly dipeptide.[7] The conformational space of compounds **10a** and **10c** has been assessed using NMR experiments and molecular modelling calculations, and their intra- and intermolecular interactions have been analyzed.

2. Results and discussion

2.1. Synthesis

The starting material for synthesis of compound **1** was *N*-α-acetyl-4-nitrohistidine methyl ester **2**, which contains all the atoms of the heterocyclic nucleus. Nitrohistidine **2** was prepared as described,[8] by nitration of *N*-α-acetylhistidine with fuming HNO_3 in concentrated H_2SO_4, followed by esterification with $SOCl_2$ in MeOH. Protection of the imidazole ring was necessary to avoid manipulation difficulties owing to the low solubility of **1** in organic solvents and to the acidity of the imidazole proton ($pK_a = 5.97$). In addition, the protected imidazopiperidones **I** and **II** can be considered frozen forms of the two tautomers.[9]

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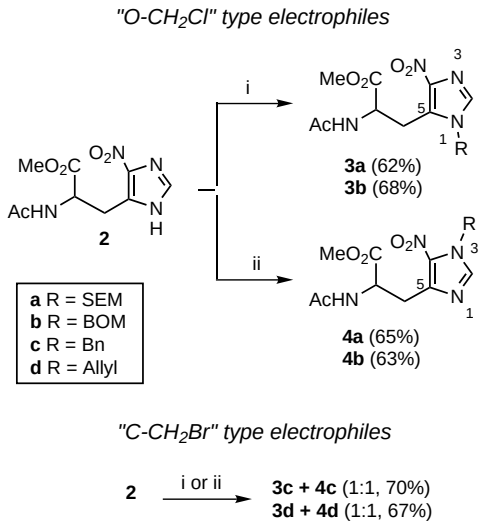
Alkylation of imidazole was carried out by treatment of compound **2** with NaH followed by addition of the alkylating reagent (Scheme 2). When **2** was treated with NaH at 0°C for 1.5 h and SEMCl then added, compound **3a** was obtained in 62% yield. However, when the reaction was conducted at room temperature, isomer **4a** was obtained in 65% yield. A similar regioselectivity was observed when BOMCl was used as the alkylating reagent. In contrast, when BnBr or allyl bromide were used as the alkylating reagents, generation of the anion using NaH at either 0°C or room temperature gave an equimolar mixture of isomers **3c**,**d** and **4c**,**d**. These results indicate that at low temperature the form of the generated anion in which the negative charge is on N-1 can be trapped by the more reactive SEMCl and BOMCl. The reaction thus appears to be kinetically controlled.

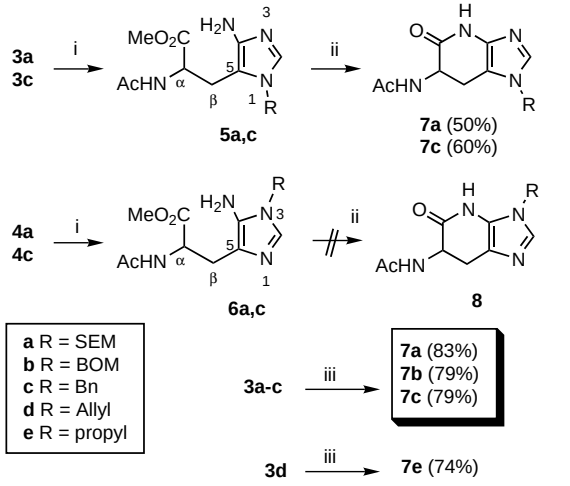


Scheme 2. *Reagents and conditions*: (i) a. NaH, DMF, 0°C, 1.5 h; b. RX, 0°C, 1 h; (ii) NaH, DMF, room temperature, 1.5 h, RX, room temperature, 1 h.

Isomers **3a**–**d** and **4a**–**d** were separated by column chromatography and fully characterized.[10] N_1- and N_3-Substituted derivatives were assigned on the basis of electronic effects, as previously reported by Giralt et al. for N_1- and N_3-methyl-*N*-α-acetyl-4-nitrohistidine methyl esters.[9b] In our case, the assignments were unambiguously corroborated by HMBC ($J^{1,3}$) and NOESY experiments on the N_1-alkylated derivatives **3**. Thus, the signals of the methylene protons of the imidazole protecting group were correlated with C-5, which proves that the methylene is linked to N_1. In the spectra of the regioisomers **4**, the methylene protons of the protecting group (linked to N_3) were correlated with C-4. In addition, NOESY experiments showed that in isomers **3**, the methylene protons of the imidazole protecting groups are close to the methylene protons of the C5 side chain.

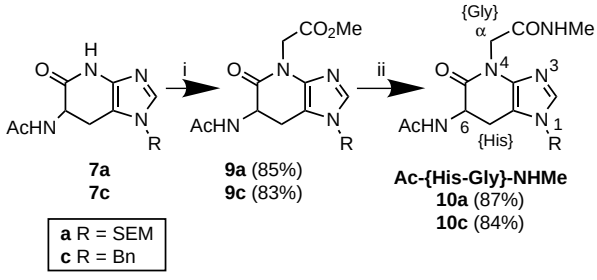
Hydrogenation of compounds **3a**,**c** and **4a**,**c** yielded aminohistidines **5a**,**c** and **6a**,**c** (Scheme 3). Heating compounds **5a** and **5c** in MeOH at reflux for 6 h led to the target lactams **7a** (50%) and **7c** (60%). However, treatment of compounds **6a** and **6c** in the same conditions did not yield the corresponding lactams **8**, due to the instability of the starting aminohistindines.[11] We therefore attempted the direct transformation of the nitrohistidines **3a**–**d** to the target lactams, and achieved this by hydrogenation at 150 psi for 24 h, in the presence of 10% Pd/C. Compound **6a** was observed to decompose when treated under these conditions.

The pseudoequatorial disposition of the acetylamino substituent on C6 was inferred from the coupling constants of the H-6 signal in the ^{1}H NMR spectra of compounds **7a** and **7c**, which appears as a double doublet of doublets ($J=13$, 8, 4.5 Hz) at δ 4.60 (**7a**) and 4.57 (**7c**).



Scheme 3. *Reagents and conditions*: (i) H_2, 10% Pd/C, MeOH, P_{atm} (70–81%); (ii) MeOH, reflux, 3 h; (iii) H_2, 10% Pd/C, MeOH, 150 psi.

The next step was to prepare compounds **9a** and **9c**, constrained surrogates of the His-Gly dipeptide, and their derivatives **10a** and **10c** (Scheme 4). Thus, treatment of compounds **7a** and **7c** with NaH followed by addition of methyl bromoacetate, yielded the corresponding esters **9a** (85%) and **9c** (83%). Transformation of compounds **9a** and **9c** to **10a** and **10c** was satisfactorily achieved using a 2 M solution of $MeNH_2$ in MeOH. The most characteristic features of compounds **10** in the ^{1}H NMR spectrum are an AB system corresponding to the diastereotopic α-protons, and two NH amide protons.[12]



Scheme 4. *Reagents and conditions*: (i) a. NaH, THF, room temperature, 1 h. b. $BrCH_2CO_2Me$, reflux, 5 h; (ii) $MeNH_2$ (2 M in MeOH), MeOH, 16 h.

2.2. Structural studies

Compounds Ac-{His-Gly}-NHMe **10a** and **10c**, which contain all the features necessary to form β- or γ-turns,[13] were used as models for structural studies. The molecule could also adopt a conformation in which the methylamide proton is intramolecularly hydrogen bonded to the N_3–imidazole nitrogen atom (Fig. 1). Using NMR to determine whether the amide protons are hydrogen bonded, as well as molecular modelling calculations, we attempted to define the most stable conformation of the system.

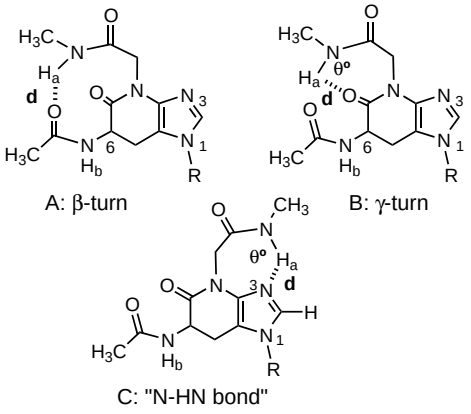


Figure 1. Three possible conformations of compounds **10**.

The influence of sample concentration on the amide protons in $CDCl_3$[14] and the solvent effect on NH chemical shift[15] were studied by NMR. From these experiments we concluded that there was neither a tendency to intermolecular aggregation[16] nor any of the intramolecular O–HN hydrogen bonds that would be observed in the presence of β- or γ-turns. However, the data suggested a slightly more stable conformation, with a weak hydrogen bond between the NHa and the N_3 imidazole nitrogen atom (conformation C).

Accordingly, molecular modelling calculations[17] showed that for compounds **10a** and **10c** the most stable conformation was C (Fig. 1), in which the distance 'd' between the NHa proton and the N_3 imidazole nitrogen atom, as well as the θ angle N_3–Ha–N, allows for an intramolecular hydrogen bond. Conformation B, with a 'd' and a θ (O–Ha–N) allowing hydrogen bonding between NHa and the oxygen atom of the lactam carbonyl, was also observed, but was less stable ($\Delta E \sim$ 2.5 kcal/mol). Conformation A was not observed, as the distance between the NHa proton and the oxygen atom of the acetyl group was always more than 5.4 Å.

3. Conclusion

6-Amino-1,4,6,7-tetrahydroimidazo[4,5-*b*]-pyridin-5-ones **7** have been prepared by protection of N_α-acetyl-4-nitrohistidine **2**, followed by reduction, and cyclization of the resulting amino substituent on the methyl ester group to build the 3-amino-2-piperidone ring. Pseudodipeptides Ac-{His-Gly}-OMe **9** and Ac-{His-Gly}-NHMe **10** have also been prepared. The structural studies performed on compounds **10** show that there is no tendency to intermolecular aggregation, and that the most stable conformation of the system is a folded conformation type C.

Acknowledgements

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10. Representative experimental procedure for compounds **3** and **4**: To a mixture of NaH (60% in mineral oil, 11.7 mmol) in DMF (2.5 mL), a solution of *N*-acetyl-4-nitrohistidine methyl ester (7.81 mmol) in DMF (5 mL) was added dropwise. After stirring for 1.5 h at 0°C, SEMCl (8.36 mmol) was added and the mixture was stirred for 1 h at this temperature. H_2O (8 mL) was added and the solvent evaporated giving a residue which was partitioned between H_2O (10 mL) and EtOAc (15 mL). The aqueous phase was extracted (EtOAc, 2×15 mL). After the organic extracts were dried ($MgSO_4$) and evaporated the residue was chromatographed (SiO_2, EtOAc:MeOH, 95:5) to give **3a** (62%) as a yellow oil. IR (KBr) 1747, 1666 cm^{-1}; ^1H NMR (COSY, 600 MHz, $CDCl_3$) δ −0.03 (s, 9H, $SiMe_3$), 0.92–0.94 (m, 2H, CH_2-$SiMe_3$), 1.93 (s, 3H, CH_3CO), 3.52–3.61 (m, 4H, OCH_2 and H-β), 3.70 (s, 3H, OCH_3), 4.78 (dd, $J=15$ and 7.6 Hz, 1H, H-α), 5.41 (d, $J=11$ Hz, 1H, OCH_2N), 5.42 (d, $J=11$ Hz, 1H, OCH_2N), 6.50 (d, $J=7.6$ Hz, 1H, NH), 7.48 (s, 1H, H-2). ^{13}C NMR (HMBC, HMQC, 75.5 MHz, $CDCl_3$) δ 1.55 ($SiMe_3$), 17.6 (CH_2SiMe_3), 22.7 (CH_3CO), 26.4 (C-β), 51.0 (OCH_3), 52.8 (C-α), 67.1 (OCH_2N), 75.1 (OCH_2N), 129.2 (C-5), 135.5 (C-2), 145.9 (C-4), 170.1 (CON), 170.7 (COO). EIMS *m*/*z* 386 (2, M^+), 371 (22), 343 (10), 311 (36), 239 (10), 73 (100). Anal. calcd for $C_{15}H_{26}N_4O_6Si$: C, 46.62; H, 6.78; N, 14.50. Found: C, 46.49; H, 7.06; N, 14.26%. Following the above general procedure but at room temperature, compound **4a** (65%) was obtained as a white solid: mp 65–66°C (isopropanol). IR (KBr) 1747, 1666 cm^{-1}; ^1H NMR (COSY, 600 MHz, $CDCl_3$) δ −0.03 (s, 9H, $SiMe_3$), 0.91–0.94 (m, 2H, CH_2-$SiMe_3$), 1.96 (s, 3H, CH_3CO), 3.42 (dd, $J=16$ and 4.5 Hz, 1H, H-β), 3.58 (dd, $J=16$ and 6 Hz, 1H, H-β), 3.59–3.64 (m, 2H, OCH_2), 3.69 (s, 3H, OCH_3), 5.04 (ddd, $J=8.2$, 6, and 4.5 Hz, 1H, H-α), 5.63 (d, $J=10$ Hz, 1H, OCH_2N), 5.66 (d, $J=10$ Hz, 1H, OCH_2N), 6.66 (d, $J=8.2$ Hz, 1H, NH), 7.62 (1H, s, H-2); ^{13}C NMR (HMBC, HMQC, 75.5 MHz, $CDCl_3$) δ 1.64 ($SiMe_3$), 17.6 (CH_2SiMe_3), 22.8 (CH_3CO), 30.8 (C-β), 50.3 (C-α), 52.3 (OCH_3), 67.4 (OCH_2), 76.5 (OCH_2N), 134.8 (C-4), 138.8 (C-2), 143.6 (C-5), 169.5 (CON), 171.4 (COO). Anal. calcd for $C_{15}H_{26}N_4O_6Si$: C, 46.62; H, 6.78; N, 14.50. Found: C, 46.55; H, 6.74; N, 14.60%.

11. The N_3-alkylated aminohistines **6a** and **6c** proved to be unstable, even when they were kept under Ar atmosphere.

12. Representative data for compound **10a**: IR (KBr) 1660 cm^{-1}; ^1H NMR (COSY, 600 MHz, $CDCl_3$) δ −0.05 (s, 9H, $SiMe_3$), 0.84–0.90 (m, 2H, CH_2-$SiMe_3$), 2.03 (s, 3H, CH_3CO), 2.66 (dd, $J=15$ and 13 Hz, 1H, H-7_{ax}), 2.79 (d, $J=4.8$ Hz, 3H, $NHCH_3$), 3.48 (t, $J=8$ Hz, 2H, OCH_2), 3.68 (dd, $J=15.6$ and 7.8 Hz, 1H, H-7_{ec}), 4.42 and 4.62 (AB_{system}, $J=16.2$ Hz, 2H, NCH_2CO), 4.67 (ddd, $J=$ 13.2, 7.8, and 4.8 Hz, 1H, H-6_{ax}), 5.14 (d, $J=11$ Hz, 1H, OCH_2N), 5.19 (d, $J=11$ Hz, 1H, OCH_2N), 5.96 (d, $J=3.6$ Hz, 1H, $NHCH_3$), 6.68 (d, $J=4.8$ Hz, 1H, NHCO), 7.29 (s, 1H, H-2). ^{13}C NMR (HMBC, HMQC, 75.5 MHz, $CDCl_3$) δ 1.42 ($SiMe_3$), 17.6 (CH_2SiMe_3), 23.1 (CH_3CO), 23.4 (C-7), 26.2 ($NHCH_3$), 45.4 (NCH_2CO), 50.4 (C-6), 66.5 (OCH_2), 74.7 (OCH_2N), 108.8 (C-7a), 133.8 (C-2), 138.8 (C-3a), 167.2 (COlactam), 167.9 (CON), 170.4 (COO). EIMS *m*/*z* 395 (5, M^+), 337 (14), 279 (12), 103 (11), 73 (100). Anal. calcd for $C_{17}H_{29}N_5O_5Si{\cdot}1/3H_2O$: C, 48.56; H, 7.49; N, 16.35. Found: 48.67; H, 7.61; N, 16.70%. HMRS calcd for $C_{17}H_{29}N_5O_5Si$: 395.1988. Found: 395.1992%.

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14. This experiment was done in $CDCl_3$ to avoid the interaction of a hydrogen-bonding solvent. The dilution limit would be given by the sensitivity of the NMR instrument (600 MHz), and the concentration limit would be set by the solubility of the sample in $CDCl_3$.

15. The experiments were done using 4 mM samples, a concentration at which no N–HN hydrogen bonding had been observed in $CDCl_3$, and consisted of running the spectra in a gradient of DMSO in $CDCl_3$ and observing the NH chemical shift.

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17. Calculations were made assuming in vacuo conditions, using SPARTAN SGI v 5.1.3 Open GL.