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# The homologation of histidine

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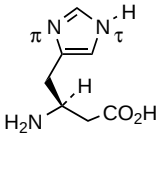
**Abstract**—(*S*)-3-Amino-4-[(1*H*)imidazol-4-yl]butanoic acid (**1**), a β-amino acid which is a homologue of L-histidine, has been synthesised in five steps from L-histidine methyl ester. The presence of *N*(α)- and *N*(Im)-2,4,6-trimethylbenzenesulfonyl protecting groups was crucial to the success of the route, the key step of which involved the ring opening of an aziridine intermediate by sodium cyanide. 

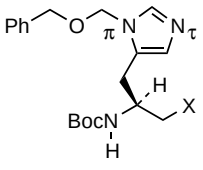
There is currently much interest in preparing β-amino acids as unnatural analogues of biologically important α-amino acids.[1] In many cases this can by achieved by homologation of the appropriate α-amino acid, e.g. by using a Wolff rearrangement of the diazo ketone (Arndt–Eistert approach)[2] or by reduction to the *N*(α)-protected amino alcohol, the hydroxyl group of which is then activated and converted into the corresponding cyanide; this is then hydrolysed to give the new carboxylic acid.[3]

Histidine is a remarkable amino acid, in which the basic imidazole side chain is crucial to the biological activity of many proteins and peptides. It is notable that the homologation of histidine to give the β-amino acid **1** has not hitherto been reported. The nucleophilic character of the unprotected imidazole ring can be expected to be a source of difficulty in the usual approaches to homologation, which involve transformation of the carboxyl group into a strong electrophile. Nevertheless we considered that suitable protection of the imidazole ring would make it possible to achieve homologation via the cyanide route. We now describe a study of protection strategies for histidine and histidinol, culminating in a synthesis of the histidine β-homologue **1**.

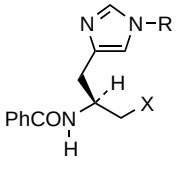
L-Histidinol is expensive and its highly polar nature makes its isolation awkward. Consequently, it was thought best to start the synthesis from L-histidine and to introduce some protection prior to the formation of the alcohol by reduction. The *N*(α)-Boc, *N*(π)-Bom protecting group combination devised by Jones[4] has proved effective in the synthesis of histidine-containing peptides. When this set of protecting groups was used in the homologation sequence, attempts to activate alcohol **2a** as its tosylate[†] ester **2b** (TsCl, pyridine, 4-pyrrolidinopyridine, room temp, 1 day) did not yield an isolable single product. Treatment of the crude product from this reaction with sodium azide in DMF did however provide a low yield of the azide **2c**. Difficulties were also encountered during homologation attempts using *N*(α)-benzoyl protection. Tosylation of alcohol **3a** (TsCl, Py, 0°C, 2 h) failed to give the desired product **3c**, but led to the formation of a mixture



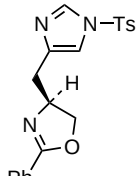
**1**



**2a** X = OH
**2b** X = OTs
**2c** X = $N_3$



**3a** R = H, X = OH
**3b** R = Ts, X= OH
**3c** R = Ts, X = OTs



**4**

*Keywords*: amino acids and derivatives; aziridines; imidazoles; protecting groups.

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† Tosyl = toluene-4-sulfonyl = Ts.

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containing the oxazoline **4** (34%), the *N*-tosylated alcohol **3b** (22%) and another product which could not be isolated but which appeared by $^1$H NMR to be an imidazolium salt.

At this point it was concluded that the risk of intramolecular nucleophilic attack on any activated intermediate needed to be kept to a minimum and so it was decided to introduce powerfully electron withdrawing arylsulfonyl groups onto both the imidazole ring and the α-nitrogen.

The 2,4,6-trimethylbenzenesulfonyl (mesitylenesulfonyl, Mts) group has been reported to be effective for protecting imidazole nitrogen during a synthesis of β-methyl-L-histidine which involved exposure to electrophilic, basic and nucleophilic reagents.[5] Mts has also been shown to be a potential protecting group for aliphatic primary amines,[6] but optimum deprotection conditions do not appear to have been identified and we are not aware of any application to multi-step synthesis. Treatment of L-histidine methyl ester dihydrochloride (**5**) with MtsCl in the presence of triethylamine yielded Mts-His(τ-Mts)-OMe **6** (81%). We were encouraged to find that acidolysis of **6** (48% aq. HBr, excess PhOH, 110°C, 18 h) gave efficient cleavage of all the protecting groups and formation of histidine.

Reduction of the methyl ester **6** to give alcohol **7** was achieved in 58% yield using $NaBH_4$ in MeOH. Other hydride reducing agents which were also tried: $LiAlH_4$ in THF at room temperature gave **7** in 26% yield along with polar by-products which are thought to arise by reductive cleavage of the *N*(τ)-Mts group; $LiBH_4$ in THF also gave a complex mixture.

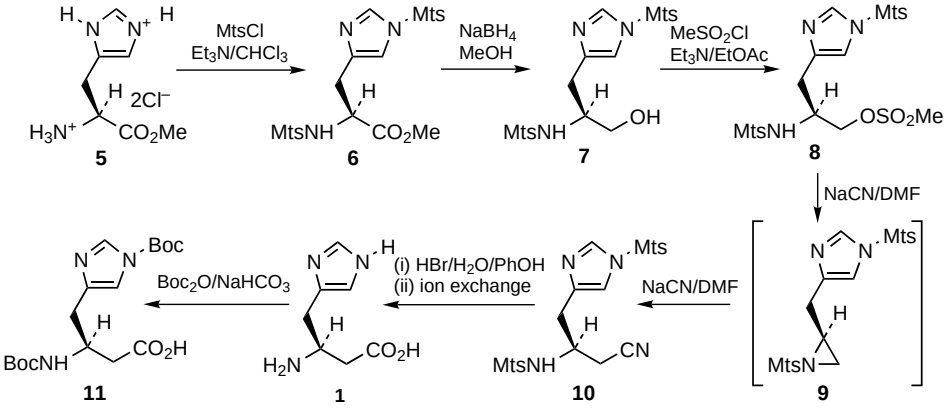
Alcohol **7** was activated as its methanesulfonate ester **8** (81%); small amounts of the aziridine **9** were also produced in this reaction.[7] Treatment of the methanesulfonate **8** with NaCN (1 equiv.) in DMF at room temperature gave mainly the aziridine **9**, which could be ring-opened by excess cyanide to give the desired nitrile **10**. By using two or more equivalents of NaCN in DMF at room temperature the methanesulfonate **8** could be converted into the nitrile **10** (63%) in a single step. Acid hydrolysis of nitrile **10** (48% aqueous HBr, phenol, 102°C, 78 h in total; some mechanical losses were incurred because the acidolysis was first worked up after 14 h when the relatively insoluble *N*(α)-Mts derivative of **1** was still present) then gave the deprotected histidine homologue **1**. Purification of **1** was performed by extraction of an aqueous solution with $CH_2Cl_2$, which removed residues derived from phenol and from the cleaved Mts groups; this was followed by anion exchange to remove ammonium bromide and HBr. Freeze-drying gave the β-amino acid **1** as a hygroscopic white solid which retained acetic acid used in the ion exchange chromatography. The $^1$H NMR chemical shifts, particularly of Im 2-H, depended on the amount of acid present. Treatment of **1** with $Boc_2O$ and $NaHCO_3$ gave the oily *N*(α),*N*(τ)-bis(Boc) derivative **11** which was then transformed into its crystalline dicyclohexylammonium salt (23% yield from nitrile **10**). This salt is suitable for direct use in the synthesis of peptides.[8]

In conclusion, we have found that *N*-Mts groups possess sufficient electron-withdrawing ability and acid lability to protect both the primary amino and imidazole functions of histidine during its transformation into the β-homologue **1** via the electrophilic intermediates **8** and **9**. However, the deprotection of *N*(α)-Mts is somewhat harsh and it would be advantageous to identify an alternative protecting group which is easier to remove, ideally one which could also be used in peptide synthesis.

## Selected experimental procedures and spectroscopic data

*(S)-4-[1-(Toluene-4-sulfonyl)-(1H)imidazol-4-ylmethyl]-4,5-dihydro-1,3-oxazole* (***4***): White crystalline solid, mp 139–141°C (from $CH_2Cl_2$–$Et_2O$), $[\alpha]_D$ −32 (*c* 1.03, $CH_2Cl_2$). $\delta_H$ (250 MHz, $CDCl_3$) 7.92 (d, 1H, *J* 1 Hz), 7.88–7.91 (m, 2H), 7.75 (d, 2H, *J* 8 Hz), 7.52–7.36 (m, 3H), 7.28 (d, 2H, *J* 8 Hz), 7.12 (d, 1H, *J* 1 Hz), 4.65–4.53 (m, 1H), 4.43 (dd, 1H *J* 9, 8 Hz), 4.19 (dd, 1H, *J* 8, 7 Hz), 3.04 (dd, 1H, *J* 15, 5 Hz), 2.75 (dd, 1H, *J* 15, 8 Hz), 2.42 (s, 3H); *m*/*z* (FAB) found 382.1218, $C_{20}H_{20}N_3O_3S$ ($M^+$+H) requires 382.1225; $\nu_{max}$ (film) 1649, 1377, 1173 cm$^{-1}$.

*N(α), N(τ)-Bis(2,4,6-trimethylbenzenesulfonyl)-L-histidine methyl ester* (***6***): Colourless prisms [from



$CH_2Cl_2$–$Et_2O$–petrol (bp 40–60°C)] as **6**·$CH_2Cl_2$, mp 79–80°C; $[\alpha]_D^{24}$ +12.8 (*c* 1.07, $CH_2Cl_2$). Found: C, 50.80; H, 5.57; N, 6.78. $C_{25}H_{31}N_3O_6S_2$·$CH_2Cl_2$ requires C, 50.48; H, 5.38; N, 6.79. $\delta_H$ (270 MHz, $CDCl_3$) 7.80 (s, 1H), 7.00 (s, 2H), 6.89 (s, 2H), 6.79 (s, 1H), 5.81 (d, 1H, *J* 8 Hz), 5.28 (s, 2H, $CH_2Cl_2$), 4.14–4.22 (m, 1H), 3.48 (s, 3H), 2.93 (dd, 1H, *J* 15, 6 Hz), 2.86 (dd, 1H, *J* 15, 5 Hz), 2.56 (s, 6H), 2.55 (s, 6H), 2.31 (s, 3H), 2.27 (s, 3H); *m*/*z* (FAB) found: 534.1730, $C_{25}H_{32}N_3O_6S_2$ ($M^+$+H) requires 534.1733; IR (KBr): 3306, 1746, 1367, 1175 $cm^{-1}$.

*N(α), N(τ)-Bis(2,4,6-trimethylbenzenesulfonyl)-L-histidinol* (**7**): A solution of *N*(α), *N*(τ)-bis(2,4,6-trimethylbenzenesulfonyl)-L-histidine methyl ester (**6**) (10.0 g, 18.7 mmol) in dry MeOH (180 mL) was cooled to 0°C and treated with solid $NaBH_4$ (16 g, 0.42 mol) added in small portions during 20 min. The consumption of the ester **6** was monitored by TLC [$CHCl_3$–MeOH (19:1)]; after 90 min the reaction was considered to be complete. The MeOH was evaporated and the residue was treated with water (100 ml) followed by 2 M hydrochloric acid to pH 7. The product was extracted into $CHCl_3$ (5×30 mL) and purified by flash chromatography [$CHCl_3$–MeOH (99:1)] to yield **7** (5.49 g, 58%) as a colourless foam; $[\alpha]_D^{26}$ +26.6 (*c* 1.0, $CH_2Cl_2$). $\delta_H$ (270 MHz, $CDCl_3$) 7.87 (s, 1H), 7.03 (s, 2H), 6.91 (s, 2H), 6.79 (s, 1H), 5.53 (d, 1H, *J*=8 Hz), 3.59–3.37 (m, 4H), 2.8–2.6 (m, 2H), 2.58 (s, 12H), 2.34 (s, 3H), 2.29 (s, 3H); *m*/*z* (FAB) found: 506.1767, $C_{24}H_{32}S_2N_3O_5$ ($M^+$+H) requires 506.1783; $\nu_{max}$ (film) 3306, 1603, 1369, 1175 $cm^{-1}$.

*4-[3-(Methanesulfonyloxy)-2-(2,4,6-trimethylbenzenesulfonamido)propyl]-1-(2,4,6-trimethylbenzenesulfonyl)imidazole* (**8**): A solution of the alcohol **7** (0.991 g, 1.96 mmol) in EtOAc (2 mL) was cooled to 0°C and treated with $Et_3N$ (0.64 mL, 4.6 mmol) followed by $CH_3SO_2Cl$ (0.30 mL, 3.8 mmol). The mixture was stirred for 90 min at room temperature and then purified by flash chromatography [$CH_2Cl_2$–EtOAc (9:1)] to give **8** (0.923 g, 81%) as a colourless foam; $[\alpha]_D^{26}$ −7.1 (*c* 0.42, $CH_2Cl_2$). Found: C, 51.44; H, 5.47; N, 6.91. $C_{25}H_{33}N_3O_7S_3$ requires C, 51.44; H, 5.70; N, 7.20. $\delta_H$ (270 MHz, $CDCl_3$) 7.82 (s, 1H), 7.01 (s, 2H), 6.92 (s, 2H), 6.88 (s, 1H), 6.15 (d, 1H, *J* 8 Hz), 4.17 (dd, 1H, *J* 10, 4 Hz), 4.00 (dd, 1H, *J* 10, 8 Hz), 3.78–3.66 (m, 1H), 2.93 (s, 3H), 2.70 (dd, 1H, *J* 15, 5 Hz), 2.60 (s, 6H), 2.57 (s, 6H), 2.6–2.5 (m, 1H), 2.32 (s, 3H), 2.29 (3H, s); *m*/*z* (FAB) found: 584.1574, $C_{25}H_{34}N_3O_7S_3$ ($M^+$+H) requires 584.1559; $\nu_{max}$ (film) 1603, 1358, 1175 $cm^{-1}$.

*(S)-4-[1-(2,4,6-Trimethylbenzenesulfonyl)aziridin-2-ylmethyl]-1-(2,4,6-trimethylbenzenesulfonyl)imidazole* (**9**): White foam, turning yellow on storage at room temperature, $\delta_H$ (270 MHz, $CDCl_3$) 7.83 (d, 1H, *J* 1 Hz), 7.07 (d, 1H, *J* 1 Hz), 7.00 (s, 2H), 6.92 (s, 2H), 3.07–2.97 (m, 1H), 2.88 (dd, 1H, *J* 16, 5 Hz), 2.70–2.51 (m, 14H), 2.32 (s, 3H), 2.31 (s, 3H), 2.08 (d, 1H, *J* 4 Hz); *m*/*z* (FAB) found: 488.1692. $C_{24}H_{30}N_3O_4S_2$ ($M^+$+H) requires 488.1678.

*(S)-3-(2,4,6-Trimethylbenzenesulfonamido)-4-[1-(2,4,6-trimethylbenzenesulfonyl)-imidazol-4-yl]butanonitrile* (**10**): A solution of the mesylate **8** (144 mg, 0.246 mmol) in DMF (1.5 mL) was treated with NaCN (30 mg, 0.612 mmol) and stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (4 mL) and washed with brine (5×6 mL). The EtOAc solution was then dried ($MgSO_4$), filtered and evaporated to leave a residue which was purified by flash chromatography [$CH_2Cl_2$–EtOAc (93:7) to (88:12)] to give **10** (80 mg, 63%) as a colourless foam; $[\alpha]_D^{24}$ +4.2 (*c* 0.71, $CH_2Cl_2$). $\delta_H$ (250 MHz, $CDCl_3$) 7.87 (d, 1H, *J*=1.2 Hz), 7.03 (s, 2H), 6.94 (br s, 3H), 6.33 (d, 1H, *J*=8 Hz), 3.85–3.7 (m, 1H), 2.9–2.6 (m, 3H), 2.62 (s, 6H), 2.59 (s, 6H), 2.35 (dd, 1H, *J* 17, 9 Hz), 2.33 (s, 3H), 2.30 (s, 3H); *m*/*z* (FAB) found 515.1800. $C_{25}H_{31}N_4O_4S_2$ ($M^+$+H) requires 515.1787; IR (film): $\nu_{max}$ (film) 3292, 2251, 1603, 1369, 1175 $cm^{-1}$.

*(S)-3-Amino-4-[(1H)imidazol-4-yl]butanoic acid* (**1**): The nitrile **10** (0.646 g, 1.26 mmol), 48% aqueous HBr (10 mL) and phenol (1.18 g, 12.5 mmol) were heated together at 102°C for a total of 78 h. The mixture was then diluted with $H_2O$ (40 mL) and washed with $CH_2Cl_2$ (6×20 mL). The aqueous phase was concentrated in vacuo and re-evaporated from water; the residue was dried over KOH and $P_2O_5$ and applied to a column of Amberlite® IRA-400 anion exchange resin ($OH^-$ form), which was eluted first with $H_2O$ followed by 1 M aqueous AcOH. Pooling and evaporation of ninhydrin-positive fractions, followed by dissolution in water and freeze-drying **1** (78.4 mg) as a hygroscopic foam which retained AcOH (ca. 0.33 equiv.) as determined by $^1H$ NMR. $\delta_H$ (270 MHz, $D_2O$) 8.18 (s, 1H), 7.29 (s, 1H), 3.94–3.8 (m, 1H), 3.26–3.05 (m, 2H), 2.69 (dd, 1H, *J*=17, 5 Hz), 2.56 (dd, 1H, *J*=17, 8 Hz), 2.02 (s, 1H, 0.33$AcO^-$); *m*/*z* (FAB) found: 192.0753. $C_7H_{11}N_3O_2Na$ ($M^+$+Na) requires 192.0749. The entire product was used for the following experiment.

*(S)-3-tert-Butoxycarbonylamino-4-[1-tert-butoxycarbonyl-(1H)-imidazol-4-yl]butanoic acid dicyclohexylammonium salt* (**11**·*DCHA*): The product **1** from the preceding experiment was dissolved in water (1 mL), cooled in an ice bath and treated with $NaHCO_3$ (63 mg, 0.75 mmol) followed by di-*tert*-butyl dicarbonate (272 mg, 1.25 mmol) in 1,4-dioxane (1 mL). The mixture was allowed to attain room temperature overnight and was then diluted with water (10 mL) and washed with petrol (bp 40–60°C; 3×10 mL). The aqueous phase was covered with EtOAc (10 mL), cooled to 0°C and carefully acidified to pH 3 using aq. $KHSO_4$. The layers were separated and the aqueous phase was extracted with more EtOAc (2×10 mL). The organic extracts were combined, dried ($MgSO_4$) and evaporated to leave **11** as an oily product (0.123 g) which was dissolved in $Et_2O$ (7 mL), filtered, concentrated to 1 mL and treated with *N*,*N*-dicyclohexylamine (66 μL, 0.33 mmol). Addition of petrol yielded **11**·DCHA (163 mg, 23% from nitrile **10**) as white crystals, mp 131–133°C, $[\alpha]_D^{28}$ −7 (*c* 1.6, $CHCl_3$). Found: C, 62.01; H, 8.90; N, 9.93. $C_{29}H_{50}N_4O_6$·$0.5H_2O$ requires C, 62.23; H, 9.18; N, 10.00%; $\delta_H$ (250 MHz, $CDCl_3$) 8.00 (s, 1H), 7.17 (s,

1H), 6.92 (v br s, not integrable), 6.06 (br s, 1H), 4.08 (q, 1H, *J* 7 Hz), 2.97–2.76 (m, 4H), 2.50–2.36 (m, 2H), 2.07–1.94 (m, 4H), 1.86–1.72 (m, 2H), 1.7–1.6 (m, 2H) 1.60 (s, 9H), 1.42 (s, 9H), 1.4–1.1 (m, 12H); *m*/*z* (FAB) found: 370.1978. $C_{17}H_{28}N_3O_6$ [$M^+$+H from **11**] requires 370.1960; $\nu_{max}$ 3390, 1755, 1711, 1391 $cm^{-1}$.

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