Synthesis of 5-Amino-4-aminocarbonyl-1-hydroxyimidazole and its Conversion to Novel Acyclic Analogues of AICA Riboside

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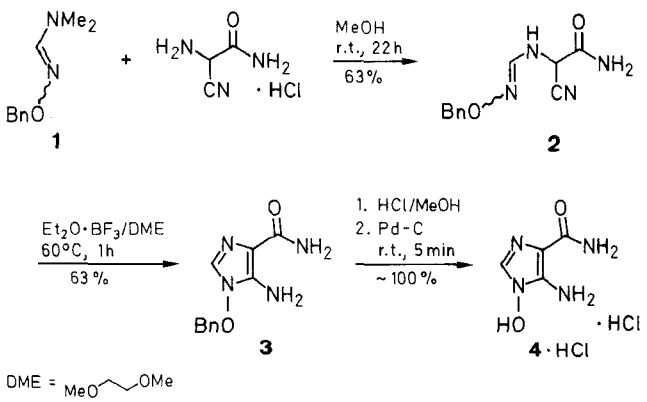
A new, improved procedure for the preparation of 5-amino-4-aminocarbonyl-1-hydroxyimidazole from *N'*-benzyloxy-*N,N*-dimethylformamidine and 2-amino-2-cyanoacetamide is described. *O*-Alkylation of this 1-hydroxyimidazole with appropriately functionalised alkyl halides or sulphonates provides an efficient route to acyclic imidazole nucleoside analogues.

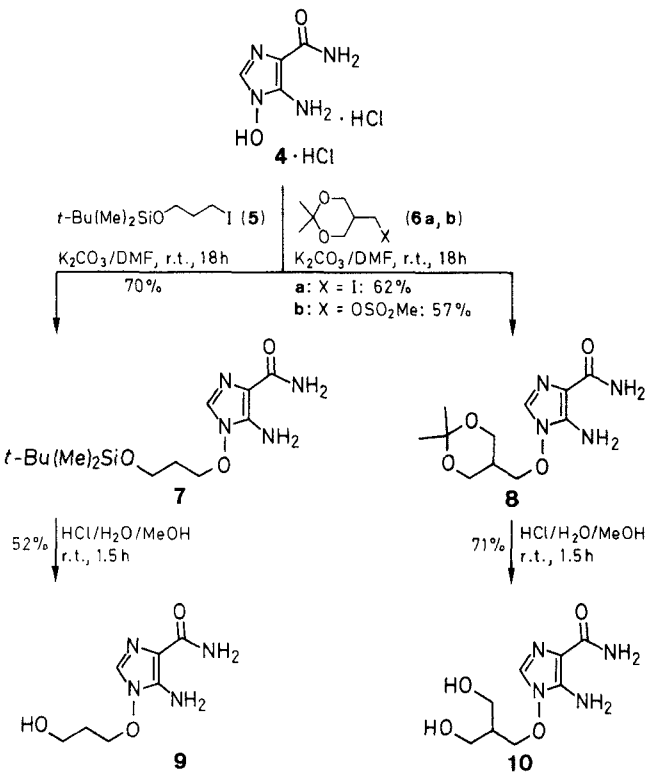
As part of our research into novel nucleoside analogues, we have recently described the synthesis of a series of purine and pyrimidine derivatives in which an acyclic moiety is attached to the heterocyclic base by means of an N–O bond.[1-5] The outstanding antiherpes virus activities of the purine derivatives in this series have been reported.[3,4]

In connection with this work, we were interested in developing an efficient synthesis of analogous acyclic derivatives of 5-amino-4-aminocarbonylimidazole (AICA). In addition to being synthetic intermediates for antivirally active purines,[1-3,6] such derivatives are of interest as potential inhibitors of enzymes involved in nucleic acid biosynthesis because of their structural resemblance to the purine nucleotide precursor AICA-riboside. In this publication we describe the preparation of two such analogues, **9** and **10**, by alkylation of 5-amino-4-aminocarbonyl-1-hydroxyimidazole **(4)** with appropriately functionalised alkyl halides or sulphonates.

Synthesis of **4** by direct oxidation of AICA has not yet been achieved. The protected imidazole **3**, a useful intermediate in the synthesis of purine *N*-oxides, has previously been prepared in only 15% yield by reaction of benzyloxyamine hydrochloride with ethyl *N*-[aminocarbonyl(cyano)methyl]formimidate.[7] We have devised an improved route for the preparation of **3** via the reaction of 2-amino-2-cyanoacetamide hydrochloride with the formamidine derivative **1** (*N,N*-dimethyl-*N'*-benzyloxymethanimidamide) in methanol at room temperature. The intermediate **2** (postulated but not isolated in the literature procedure[7]) was obtained in 63% yield as a pale amber solid. This material, although unstable at room temperature, especially in solution, could be stored at −20 °C for prolonged periods. Cyclisation of **2** in methanolic hydrogen chloride gave the imidazole **3** in 24% yield. No improvement on this yield was observed on treatment with other mineral acids, or by varying the solvent. However, when **2** was treated with the Lewis acid diethyl ether–boron trifluoride in 1,2-dimethoxyethane at 60 °C, cyclisation occurred cleanly to give **3** in 63% yield. Deprotection of **3** using catalytic hydrogenolysis over 10% palladium on charcoal afforded a quantitative yield of **4** isolated as its hydrochloride.

Alkylation of **4**, as its hydrochloride salt, with the appropriately functionalised iodides, 3-*tert*-butyldimethylsiloxy-1-iodopropane[8] **(5)** or 5-iodomethyl-2,2-dimethyl-1,3-dioxane[9] **(6a)**, in the presence of potassium carbonate in dry dimethylformamide at ambient temperature gave the 1-alkoxyimidazoles **7** and **8** in 70% and 62% yield, respectively. A similar yield of **8** was obtained by using the mesylate **6b** (a precursor to **6a**) and catalytic amounts of lithium iodide at 70 °C. Both compounds **7** and **8** were deprotected under acidic conditions to give the imidazol-1-yloxyalcohols **9** and **10** in 52% and 71% yields.





2-Amino-2-cyanoacetamide was obtained from MERCK-Schuchart and crystallised from MeOH before use. The iodides **5**[8] and **6a**[9] were obtained from the corresponding alcohols by conventional treatment of their methanesulphonates with sodium iodide in acetone.

N,N-Dimethyl-N'-benzyloxymethanimidamide (N'-Benzyloxy-N,N-dimethylformamidine, 1):

A solution of *O*-benzylhydroxylamine (15.13 g, 123 mmol) in dimethylformamide dimethyl acetal (60 mL) is stirred at r.t. for 30 min. The solvent is evaporated at reduced pressure and the residue

dissolved in CH_2Cl_2 (150 mL). This solution is washed with H_2O (2 × 50 mL), dried, ($MgSO_4$), and evaporated at reduced pressure to give **1** as a colourless oil; yield: 21 g (96%).

$C_{10}H_{14}N_{20}$	calc.	C 67.39	H 7.92	N 15.72
(178.2)	found	67.09	7.78	15.55

MS (70 eV): m/z = 178 (M^+).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.75 (s, 6H, $2CH_3$), 4.90 (s, 2H, CH_2), 7.40 (m, 5H_{arom}), 7.73 (s, 1H, CH).

2-Cyano-2-[(benzyloxyimino)methyl]aminoacetamide (2):
A solution of 2-amino-2-cyanoacetamide hydrochloride (5.38 g, 40 mmol) and *N,N*-dimethyl-*N'*-benzyloxymethanimidamide (**1**; 9.3 g, 52 mmol) in MeOH (40 mL) is stirred at r.t. for 22 h. The solvent is evaporated at reduced pressure and the residual light brown oil is partitioned between EtOAc (150 mL) and H_2O (5 mL) with vigorous shaking. The organic phase is separated, washed with H_2O (2 × 5 mL), dried ($MgSO_4$), and evaporated. The residual light brown oil is extracted by vigorous shaking with hexane (2 × 150 mL) to remove unreacted **1**. The hexane extracts are decanted from the gummy product and last traces of hexane are removed by evaporation at reduced pressure. The residual gum is dissolved in warm $CHCl_3$ (ca. 50 mL) and cooled at −20°C (freezer) overnight. The product precipitates out as a pale amber solid, which is a mixture of geometric isomers, and is filtered off, washed several times with hexane, and air-dried. If not used immediately, this solid is stored at −20°C; yield: 5.87 g (63%).

$C_{11}H_{12}N_4O_2 \cdot 0.25\ H_2O$	calc.	C 55.80	H 5.32	N 23.67
(236.7)	found	55.43	5.21	23.65

MS (70 eV): m/z = 232 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 4.81 (s, 0.25H, CH_2), 4.92 (s, 1.75H, CH_2), 5.06 (d, J = 8.5 Hz, 0.12H, CH), 5.25 (d, J = 8.5 Hz, 0.88H, CH), 6.80 (d, J = 10.5 Hz, 1H, CH), 7.08 (dd, J = 8.5, 10.5 Hz, 1H, NH), 7.2–7.9 (m, 7H, C_6H_5 + NH_2), 7.7 (br s, 2H, NH_2).

5-Amino-4-aminocarbonyl-1-benzyloxyimidazole (3):
To a solution of 2-cyano-2-[(benzyloxyamino)methyl]aminoacetamide (**2**; 1.45 g, 6.3 mmol) in 1,2-dimethoxyethane (150 mL) under dry N_2 is added $Et_2O \cdot BF_3$ (0.85 mL, 6.9 mmol), and the solution is heated at 60°C in an oil bath for 1 h. The solvent is evaporated at reduced pressure and the solid residue is partitioned between $CHCl_3$ (100 mL) and saturated $NaHCO_3$ solution (100 mL), with vigorous shaking. Additional product is obtained by extracting the insoluble material in the aqueous phase with $CHCl_3$ (2 × 30 mL) on a steam bath. The combined organic phases are dried ($MgSO_4$) and evaporated and the residue is column chromatographed on silica gel ($CHCl_3$/MeOH; 10:1) to give **3** as a solid; yield: 0.92 g (63%); mp 173–174°C (EtOH) (Lit.[7] mp 168–169°C).

$C_{11}H_{12}N_4O_2$	calc.	C 56.89	H 5.21	N 24.12
(232.2)	found	56.61	5.03	24.29

MS (70 eV): m/z = 232 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.20 (s, 2H, CH_2), 5.90 (br s, 2H, NH_2), 6.77 (br s, 2H, $CONH_2$), 7.19 (s, 1H, 2_{im}-H), 7.50 (m, 5H_{arom}).

5-Amino-4-aminocarbonyl-1-hydroxyimidazole (4):
A solution of 5-amino-4-aminocarbonyl-1-benzyloxyimidazole (**3**; 460 mg, 2 mmol) in MeOH (10 mL), under N_2 is treated with sat. methanolic HCl (2 mL) and 10% Pd-C (200 mg). The mixture is then hydrogenated at ambient temperature and pressure until H_2 uptake ceases (5 min). The catalyst is filtered off and the solvent is evaporated at reduced pressure to give **4** as a solid which is converted to its hydrochloride by treatment with sat. methanolic HCl; yield: 0.35 g (100%); mp > 300°C (HCl/EtOH).

$C_4H_7ClN_4O_2$	calc.	C 26.90	H 3.95	N 31.37
(178.6)	found	26.99	4.02	31.61

MS (70 eV): m/z = 142 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.5–8.5 (br, 6H, NH_2, $CONH_2$, OH, HCl), 8.95 (1H, s, 2_{im}-H).

5-Amino-4-aminocarbonyl-1-(3-*tert*-butyldimethylsiloxy)propoxyimidazole (7) and 5-Amino-4-aminocarbonyl-1-(2,2-dimethyl-1,3-dioxan-5-yl)methoxyimidazole (8); General Procedure:
A mixture of 5-amino-4-aminocarbonyl-1-hydroxyimidazole hydrochloride (**4** · HCl; 350 mg, 1.9 mmol), iodide **5** or **6a** (2.2 mmol), and K_2CO_3 (550 mg, 4.0 mmol) in dry DMF (50 mL) is stirred at r.t. for 18 h. The insoluble material is removed by filtration and the filtrate is evaporated at reduced pressure. The residue is column chromatographed on silica gel (MeOH/CH_2Cl_2; 5:95), then crystallised from EtOH to give the 1-alkoxyimidazoles **7** or **8**, respectively.

Compound **7**: yield: 0.43 g (70%); mp 158.5–159.5°C.

$C_{13}H_{26}N_4O_3Si$	calc.	C 49.65	H 8.33	N 17.81
(314.4)	found	49.72	8.42	17.68

MS (70 eV): m/z = 314 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 0.05 (s, 6H, $2CH_3Si$), 0.86 (s, 9H, $3CH_3C$), 1.88 (m, 2H, J = 6.3 Hz, CH_2), 3.73 (t, 2H, J = 6.3 Hz, CH_2), 4.20 (t, 2H, J = 6.3 Hz, CH_2), 5.8 (br s, 2H, NH_2), 6.7 (br s, 2H, $CONH_2$), 7.3 (s, 1H, 2_{im}-H).

Compound **8**: yield: 0.5 g (62%); mp 173.5–175°C (dec).

$C_{11}H_{18}N_4O_4$	calc.	C 48.87	H 6.71	N 20.73
(270.3)	found	48.81	6.87	20.44

MS (70 eV): m/z = 270 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.32, 1.35 (2s, 3H, each, $2CH_3$), 2.06 (m, 1H, CH), 3.76 (m, 2H, CH_2), 4.0 (m, 2H, CH_2), 4.2 (d, 2H, J = 6.8 Hz, CH_2), 5.82 (br s, 2H, NH_2), 6.76 (br s, 2H, $CONH_2$), 7.44 (s, 1H, 2_{im}-H).

5-Amino-4-aminocarbonyl-1-(2,2-dimethyl-1,3-dioxan-5-yl)methoxyimidazole (8):
A mixture of 5-amino-4-aminocarbonyl-1-hydroxyimidazole hydrochloride (**4** · HCl; 1.79 g, 10 mmol), 2,2-dimethyl-1,3-dioxan-5-ylmethyl methanesulphonate (**6b**; 2.47 g, 11 mmol), K_2CO_3 (2.77 g, 20 mmol), and LiI (0.15 g, 1.1 mmol) in dry DMF (75 mL) is heated to 70°C for 5 h. The cooled mixture is filtered, the solvent is evaporated at reduced pressure, and the residue is column chromatographed on silica gel (MeOH/CH_2Cl_2; 5:95) Crystallisation from EtOH gives **7** identical in all respects with the material obtained via the iodide; yield: 1.55 g (57%).

5-Amino-4-aminocarbonyl-1-(3-hydroxypropoxy)imidazole (9) and 5-Amino-4-aminocarbonyl-1-(3-hydroxy-2-hydroxymethylpropoxy)-imidazole (10); General Procedure:
A solution of 5M aq HCl (5 mL) is added to a stirred solution of compound **7** or **8** (4.3 mmol) in MeOH (50 mL) at r.t., and the solution is allowed to stand for 1.5 h. Amberlite IR 45 (OH) ion-exchange resin is then added to bring the pH to 7, the mixture is filtered, and the filtrate is evaporated at reduced pressure. The residue is purified by column chromatography (C18 silica gel, water). Compound **9** is converted to its hydrochloride by treatment with saturated methanolic HCl, and crystallised from EtOH. Compound **10** is crystallised from EtOH/acetone.

Compound **9** · HCl: yield: 0.15 g (52%); mp 163–165°C.

$C_7H_{13}ClN_4O_3$	calc.	C 35.52	H 5.53	N 23.67
(236.5)	found	35.46	5.54	23.42

MS (70 eV): m/z = 200 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.87 (m, 2H, CH_2), 3.35 (t, 2H, J = 6.3 Hz, CH_2), 4.33 (t, 2H, J = 6.3 Hz, CH_2), 5.75–8.0 (br, > 6H, NH_2, HCl, $CONH_2$, + H_2O), 8.6 (s, 1H, 2_{im}-H).

Compound **10**: yield 0.7 g (71%); mp 115–117°C.

$C_8H_{14}N_4O_4$	calc.	C 41.73	H 6.13	N 24.33
(230.2)	found	41.24	6.14	24.13

MS (70 eV): m/z = 230 (M^+).

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.0 (m, 1H, CH), 3.5 (m, 4H, $2CH_2$), 4.2 (d, 2H, J = 6.3 Hz, CH_2), 4.67 (t, 2H, J = 5.3 Hz, 2OH), 5.8 (br s, 2H, NH_2), 6.7 (br s, 2H, $CONH_2$), 7.4 (s, 1H, 2_{im}-H).

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