Synthesis and Characterization of 6-Carbamoyl-1,2-dihydropurines

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Abstract: The aromatic amines react readily with (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (**4**) to give the amidines (**5a-b**), which cyclize in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to give the corresponding 2-(5-Amino-1-phenyl-1*H*-imidazol-4-yl)-2-iminoacetonitrile (**6a-b**), which can be isolated. In the presence of aldehyde the formimidoylimidazole lead to novel 6-carbamoyl-1,2-dihydropurines (**8a-b**). All compounds have been fully characterized by spectroscopic data.

Keywords: Formimidoylimidazole, Aromatic amines, Imidate, Diaminomaleonitrile, Purine-6-carboxamide

Introduction

Since the discovery of acyclovir great research effort has been devoted to the synthesis of new acyclic nucleoside analogues as potential anti-herpes (HSV) and anti-human cytomegalovirus (HCMV) agents,¹ potent antiviral activities have been found for 'carbo-acyclic' nucleoside analogues such as **1**,^{1,2} and purine derivatives with simple 9-hydroxyalkyl substituents, such as **2** and **3**, have biological activity³⁻⁸.

As part of a general study⁹⁻¹⁴ of the synthesis of (C-cyanoformimidoyl)imidazole-5-amines we now report the preparation and reaction of new 1-phenyl-4-(C-cyanoformimidoyl)imidazole and 1-benzyl-4-(C-cyanoformimidoyl)imidazole. These have been found to be useful intermediates for the synthesis of new compounds 9-phenyl and 9-benzyl-1, 2-dihydropurine¹⁵⁻¹⁹.

1 **2** X = NH₂ HCl; R = CH(CHMeOH)(CH₂)₅CH₃**3** X = OH; R = CH(CHMeOH)(CH₂)₅CH₃

Experimental

All solvents purified and dried using established procedures. The ¹H NMR spectra were recorded on Bruker XL 500 (500 MHz) instruments, ¹³C NMR spectra on DRX-500 AVANCE spectrometer, and IR spectra on a Shimadzu IR-470 spectrophotometer. Mass spectra were recorded on a Kratos Concept instrument. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

General procedure for the preparation of the 2-(5-Amino-1-phenyl-1H-imidazol-4-yl)-2-iminoacetonitrile (6a-b)

A suspension of the corresponding aryl-(Z)-N-[2-amino-1, 2-dicyanovinyl]formamidine (**5a-b**)⁶⁻⁸ (1.00 g) in dry ethanol (8 mL) was added DBU (9 drops). The mixture was stirred under an argon atmosphere at room temperature for 0.5-3 h. After this time, TLC showed that all the amidine had been consumed. The reaction mixture was then filtered off, washed with dry diethyl ether and dried under vacuum to give **6a-b**.

2-(5-Amino-1-phenyl-1H-imidazol-4-yl)-2-iminoacetonitrile (6a, C₁₁H₉N₅)

Recrystallization of the product from dry diethyl ether and air-dried to give yellow crystals of **6a** (0.7 g, 2.7 mmol, 71%). Mp 114-116 °C (decomp.); IR (KBr): 3420, 3360, 3210, 3290, 3160, 2200, 1650, 1590, 1550, 1365, 1260, 1210 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ = 6.64 (s, 2H, NH₂), 6.70-6.84 (m, 5H, Ar-H), 7.20 (s, 1H, H-imidazole), 9.88 (br. s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-d₆): δ = 117.4, 120.4, 128.8, 132.6, 134.0, 136.1, 137.9, 147.1, 147.9 ppm; MS (EI, 70 Ev): *m/z* (%) 212 (3.9) (M+1)⁺, 211 (13.7) (M)⁺, 78 (14.2).

2-(5-Amino-1-benzyl-1H-imidazol-4-yl)-2-iminoacetonitrile (6b, C₁₂H₁₁N₅)

Recrystallization of the product from diethyl ether give pale green crystals of **6b** (0.62 g, 2.57 mmol, 62%). M.p. 136-137 °C (decomp); IR (KBr): 3320, 3210, 3190, 2220, 2210, 1640, 1570, 1510, 1450, 1280, 860, 815, 820 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ = 5.45 (s, 2H, CH₂), 6.10 (br. s, 2H, NH₂), 6.95-7.09 (m, 5H, Ar-H), 7.14 (s, 1H, H-imidazole), 9.80 (br. s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO-d₆): δ = 49.7, 117.5, 120.2, 131.2, 131.7, 132.4, 136.4, 140.4, 147.1, 148.3 ppm; MS (EI, 70 Ev): *m/z* (%) 226 (100) (M+1)⁺, 225 (11.6) (M)⁺, 199 (20.6), 91 (20.8).

Preparation of 2-(3-nitrophenyl)-9-phenyl-2,9-dihydro-1H-purine-6-carboxamide (8a, C₁₈H₁₄N₆O₃)

A suspension of the imidazole (0.4 g, 1.8 mmol) and 3-nitrobenzaldehyde (5 cm³) in methanol (5 mL) was stirred at room temperature overnight. The orange solid was filtered, washed with diethyl ether and dried to give 2-(3-nitrophenyl)-9-phenyl-2,9-dihydro-1H-

purine-6-carboxamide (**8a**) (0.47g, 1.5 mmol, 81%). Mp 172-174 °C (decomp.); IR (KBr): 3399, 3355, 3215, 3100, (N-H str.), 2220, 2210 (CN str.), 1695 (C=O), 1660 (C=N str.), 1560 (N-H bend), 1510, 1450, 1270, 860, 800 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ= 6.85-6.97 (m, 5H, Ar-H), 7.12-7.30 (m, 3H, Ar-H), 7.50 (s, 1H, H-imidazole), 7.69-7.72 (br. s, 2H, NH₂), 9.60 (br. s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO- d₆): δ=76.2, 136.4, 122.2, 159.8, 148.4, 166.4, 124.4-124.5 ppm; MS (EI, 70 Ev): *m/z* (%) 363 (65.5) (M+1)⁺, 362 (78) (M)⁺, 346 (18.4), 318 (90.6), 316 (60.5), 272 (17.6), 196 (34), 119 (25.1).

Preparation of 9-benzyl-2-(3-nitrophenyl)-2, 9-dihydro-1H-purine-6-carboxamide (8b, C₁₉H₁₆N₆O₃)

A suspension of the imidazole (0.5 g, 2.2 mmol) in 3-nitrobenzaldehyde (8 cm³) was stirred at room temperature. After 20 minutes, an orange solid was started to precipitate, and reaction was complete after 3 h. Additional of the chloroform and partial removal of the solvent on the rotary evaporator led to an orange solid, which was washed with chloroform and diethyl ether, and identified as 9-benzyl-2-(3-nitrophenyl)-2,9-dihydro-1H-purine-6-carboxamide (**8b**) (0.52 g, 1.6mmol, 72%). An analytical sample was obtained after flash chromatography (silica 60; dry acetone eluent) which gave bright orange crystals. M.p. 182-186 °C (decomp.); IR (KBr): 3310, 3220, 3170 (N-H str.), 2220, 2200 (CN str.), 1710 (C=O), 1630 (C=N str.), 1570 (N-H bend), 1520, 1460, 1280, 850, 810 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ= 4.95 (s, 2H, H-2), 6.92-7.00 (m, 5H, Ar-H), 7.10-7.30 (m, 4H, Ar-H), 7.42 (s, 1H, H-imidazole), 7.83-7.85 (br. s, 2H, NH₂), 9.67 (br. s, 1H, NH) ppm; ¹³C NMR (75 MHz, DMSO- d₆): δ= 24.5, 76.5, 137.2, 122.4, 160.3, 148.7, 166.8, 123.6-14.2 ppm; MS (EI, 70 Ev): *m/z* (%) 377 (91.5) (M+1)⁺, 376 (100) (M)⁺, 332 (8.9), 330 (1.8), 286 (3.2), 210 (7.6%).

Results and Discussion

Formimidate (**4**) was prepared in high yield from diaminomaleonitrile and triethyl orthoformate, according to a previously described procedure⁶⁻⁸. Having obtained the imidate (**4**) in good yield (94%) it was then treated with aryl or benzylamine in a 1:1 molar ratio in ethanol in the presence of a catalytic amount of anilinium chloride^{8,9}.

We thus attempted to cyclise the amidines **5a-b** to obtain compounds of type **6a-b**, in 78% yield by treatment with DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene) in ethanol.¹⁰⁻¹² The reaction was followed by TLC. When all the starting material had been consumed filtration and concentration of the filtrate under reduced pressure (at < 30°C) gave **6a-b** as a pale green solid which were stored under argon at low temperature. It was found that this compound darkens rapidly in solution and decomposes to black oil. Compounds **6a-b** would be important intermediates for the synthesis of a range of 9-aryl or benzylpurines and 9-aryl or benzyl-1, 2-dihydropurines⁷⁻¹².

Scheme 1. Reagents and conditions: (i) RNH₂, ArNH₃⁺ Cl⁻, (ii) DBU, EtOH, room temp.

The spectroscopy results obtained on these compounds **6a-b** were satisfactory. The ^1H NMR spectrum showed the presence of two broad singlet a 6.64 and 9.88 ppm due to the amine protons and a singlet at 7.28 for the HC proton of the imidazole ring. The ^{13}C NMR spectrum was fully consistent with the assigned structure. The infrared spectrum confirmed the presence of the NH and C=N stretching vibrations within the region of 3420-3160, and 1650-1640 cm^{-1} respectively. The infrared spectrum also showed a sharp absorption band at 2220-2200 cm^{-1} for the C≡N stretching vibration.

The dihydropurines **8a-b** were prepared by stirring a suspension of the corresponding 4-(cyanoformimidoyl)-imidazoles **6a-b** with a slight excess of 3-nitrobenzaldehyde in a small amount of ethanol or methanol at room temperature (Scheme 2). The reactions were monitored by TLC (9: 1 CHCl_3 - EtOH) and reaction times varied between 20 min and 24 h. Depending upon the solvent used for the reaction and the rate of precipitation, these dihydropurines can be isolated as solids in color from orange to yellow.

Scheme 2.

Compounds **8a-b** were recrystallised from mixture of ethanol/methanol (1:1) and gave pale yellow to off white crystals respectively. These were fully characterized by TLC, IR and ^1H NMR, ^{13}C NMR and mass spectroscopy. The infrared spectrum confirmed the presence of the NH and C=N stretching vibrations within the region of 3400-3100, and 1660-1650 cm^{-1} respectively. The C=O of the amide group appeared at 1695-1710 cm^{-1} as a strong band. The high resolution mass spectrum gave a molecular ion peak at 363, 377 ($\text{M}+1$) $^+$ which fits with the expected molecular weight of 362, 376 for the dihydropurine (**8a-b**). In the ^1H NMR spectra of the isolated compounds **8a** and **8b**, the amide protons were observed in the region of δ 7.69-7.85 ppm and in several cases the assignment were confirmed by D_2O exchange. The H-2 proton appeared as a broad singlet at δ 4.95-4.97 ppm and the aromatic protons showed the expected patterns in the range of δ 6.85-7.30 ppm. The proton of the imidazole ring appeared as a sharp singlet in the range of δ 7.42-7.50 ppm. The ^{13}C nmr spectrum of these dihydropurine had the expected number of bands, with the C-2 carbon at δ 76.2-76.5, C4 carbon at δ 136.4-137.2, C-5 carbon at δ 122.2-122.4, C-6 carbon at δ 159.8-160.3, C-8 carbon at δ 148.4-148.7, C=O carbon at δ 166.4-166.8 ppm.

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