Chapter 10
Synthesis and Characterization of 6-Carbamoyl-2-Alkyl-9-(Phenyl or Benzyl)-9*H*-Purines

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Abstract The 2-(5-amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1*H*-imidazoles proved to be important intermediates not only in the preparation of new 6-carbamoyl purines but also in the synthesis of 6-amino-purine, 6-cyano-purine and 1,2-dihydropurines. 6-Carbamoyl-2-alkyl-9-(phenyl or benzyl)-9*H*-purines have been synthesized in high yields by reactions between 2-(5-amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1*H*-imidazoles and acetylacetone at room temperature. Intramolecular hydrogen bonding appears between H of NH_2 and N1 at purine ring. All the compounds have been fully characterized by spectroscopic data.

10.1 Introduction

Purines are extremely important compounds with a wide array of synthetic and industrial applications. They are integral parts of DNA and RNA, playing an essential role in several biological processes with considerable chemical and pharmacological importance. The biological importance of the purine structure is evident from the countless derivatives that have been prepared and are active, especially as antiviral and antitumor agents [1–4]. The substituent in the 6-position plays an important role in the potency and selectivity of the purine derivatives. As a result, great efforts have been directed to the synthesis and biological evaluation of a number of 6-substituted purines.

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10.2 Experimental

10.2.1 General Techniques

All solvents were purified and dried using established procedures. The ^{1}H NMR spectra were recorded on Bruker XL 500 (500 MHz) instruments (with J-values given in Hz), and IR spectra on a Shimadzu IR-470 spectrophotometer. The melting points were measured on an Electro-thermal digital melting point apparatus with the thermometer uncorrected.

10.2.2 General Procedure for the Preparation of the 2-(5-Amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1H-imidazoles 3a-d

To a suspension of the corresponding aryl-(*Z*)-*N*-[2-amino-1,2-dicyanovinyl] formamidine **2a-d** (1.00 g) in dry ethanol (8 ml) was added DBU (9 drops) [6–8, 13]. The mixture was stirred under an argon atmosphere at room temperature for 0.5–3 h until 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 **3a-d**.

10.2.3 General Procedure for the Preparation of the 6-Carbamoyl-2-alkyl-9-(phenyl or benzyl)-9H-purines 4a-d

1,3-Dione (5 ml) was added to a solution of 2-(5-amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1*H*-imidazoles **3a-d** (0.12 g) in acetonitrile (10 ml) and the mixture was stirred at room temperature for 20–24 h. The reaction mixture was then filtered off, washed with dry diethyl ether and dried under vacuum to give **4a-d**.

Synthesis of 6-carbamoyl-2-methyl-9-(4-ethoxyphenyl)-9*H*-purine 4a: Recrystallization of the product from dry diethyl ether and air-drying gave white crystals of 6-carbamoyl-2-methyl-9-(4-ethoxyphenyl)-9*H*-purine **4a** (0.87 g, 72 %); mp 287–288 °C; Analysis: [Found: C, 59.80; H, 5.24; N, 24.10. Calc. for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.05; N, 23.56 %]; IR (KBr): 3,400 s, 3,180 s, 3,100 w, 2,980 w, 1,650 m, 1,610 m, 1,520 s, 1,480 w, 1,400 s, 1,345 w, 1,250 s, 1,220 s, 1,040 m cm^{-1}; ^{1}H NMR (DMSO) (δ ppm): 8.92 (s, 1H, H_8), 8.56 (s, br, NH), 8.06 (s, br, NH), 7.72 (d, J = 8.5 Hz, 2H, H_{10} & H_{14}), 7.14 (d, $^{3}J_{13,14}$ = 8.6 Hz, 2H, H_{11} & H_{13}), 4.10 (q, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.35 (t, 3H, CH_3); MS (EI, 70 eV): *m*/*z* (%) 298 (45) $(M + 1)^+$, 297 (100) $(M)^+$.

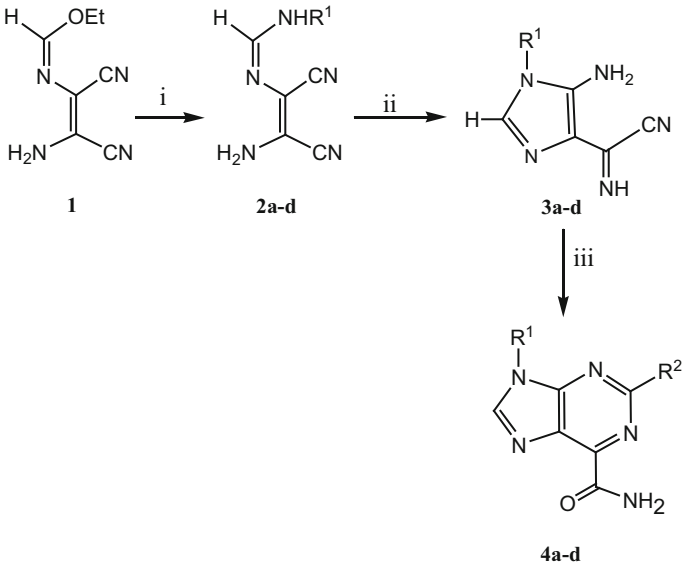
Synthesis of 6-carbamoyl-2-methyl-9-(3,4-dimethoxyphenyl)-9*H*-purine 4b: Recrystallization of the product from dry diethyl ether and air-drying gave green crystals of 6-carbamoyl-2-methyl-9-(3,4-dimethoxy phenyl)-9*H*-purine **4b** (0.84 g, 70 %); mp 218 °C; Analysis: [Found: C, 57.80; H, 4.81; N, 22.40. Calc. for $C_{15}H_{15}N_5O_3$: C, 57.50; H, 4.79; N, 22.36 %]; IR (KBr): 3,450 s, 3,380 s, 3,100 w, 1,680 m, 1,600 m, 1,520 s, 1,450 w, 1,345 w, 1,250 s, 1,220 s, 1,020 m cm^{-1}. ^1H NMR ($CDCl_3$): 8.56 (s, br, NH), 8.35 (s, 1H, H_8), 7.23 (d, J = 3.6 Hz, 1H, H_{10}), 7.16 (dd, J = 3.5 Hz, 1H, H_{14}), 7.01 (d, J = 8.5 Hz, 1H, H_{13}), 6.29 (s, br, NH), 3.95 (s, 6H, OCH_3), 2.88 (s, 3H, CH_3) ppm; MS (EI, 70 eV): *m/z* (%) 314 (24) $(M + 1)^+$, 313 (100) $(M)^+$.

Synthesis of 6-carbamoyl-9-(3,4-dimethoxybenzyl)-2-(4-isopropylphenyl)-9*H*-purine 4c: Recrystallization of the product from dry diethyl ether and air-drying gave white crystals of 9-(3,4-dimethoxybenzyl)-9*H*-purine-6-carboxamide **4c** (0.12 g, 0.27 mmol, 64 %); mp 218–219 °C; Analysis: [Found: C, 65.80; H, 6.04; N, 16.40. Calc. for $C_{24}H_{26}N_5O_3$: C, 66.66; H, 6.01; N, 16.20 %]; IR (KBr): 3,330 s, 3,200 s (N-H), 3,100 w (C-H Ar), 2,900 m (C-H aliphatic), 1,690 s (C=O), 1,650 s (C=N), 1,475 m, 1,400 m, 1,350 s, 1,250 s, 1,100 m, 1,020 m cm^{-1}; ^1H NMR (DMSO): 9.09 (s, 1H, $H_{imidazole}$), 8.59 (br. s, 1H, NH_2), 8.44 (d, 2H, J = 7.73 Hz, H_{Ar}), 8.13 (br. s, 1H, NH_2), 7.64 (s, 1H, H_{Ar}), 7.53 (d, 1H, J = 8 Hz, H_{Ar}), 7.42 (d, 2H, J = 7.72 Hz, H_{Ar}), 7.25 (d, 1H, J = 8 Hz, H_{Ar}), 3.90, 3.88 (s, 6H, 2 × OCH_3), 2.98 (m, 1H, $H_{isoprop}$), 2.53 (s, 2H, CH_2), 1.29, 1.25 (s, 6H, $2CH_3$) ppm; MS (EI, 70 eV): *m/z* (%) 433 (42) $(M + 1)^+$, 432 (87) $(M)^+$.

Synthesis of 6-carbamoyl-9-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-9*H*-purine 4d: Recrystallization of the product from dry diethyl ether and air-drying gave white crystals of 6-carbamoyl-9-(3,4-dimethoxybenzyl)-2-(3,4-dimethoxyphenyl)-9*H*-purine **4d** (0.14 g, 0.31 mmol, 74 %); mp 140–142 °C; Analysis: [Found: C, 61.65; H, 5.48; N, 16.01. Calc. for $C_{23}H_{21}N_5O_5$: C, 61.33; H, 5.33; N, 15.55 %]; IR (KBr): 3,320 s (N-H), 3,010 m (C-H Ar), 2,930 m (C-H aliphatic), 1,615 s (C=O), 1,560 s (C=N), 1,510 s (C=C), 1,475 m, 1,420 m, 1,265 s, 1,020 s, 1,140 m, 818 s, 760 s cm^{-1}; ^1H NMR (DMSO): 8.18 (s, 1H, $H_{imidazole}$), 7.84 (br. s, 1H, NH_2), 7.70 (s, 2H, H_{Ar}), 7.47 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.04 (d, 2H, J = 7.5 Hz, H_{Ar}), 3.84, 3.83 (s, 12H, 4 × OCH_3), 3.59 (s, 2H, CH_2) ppm; MS (EI, 70 eV): *m/z* (%) 451 (44) $(M + 1)^+$, 450 (88) $(M)^+$.

10.3 Results and Discussion

In our research, we have been studying the reactivity of 2-(5-amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1*H*-imidazoles **3a-d**, as versatile precursors to 6-substituted purines [2, 5–10]. Amidines **2a-d** were prepared *via* a multistep synthesis from diaminomaleonitrile [11–18]. We thus attempted to cyclise the amidines **2a-d** to obtain compounds **3a-d**, in 72–80 % yield by treating with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in ethanol [9–13] (Scheme 10.1 and Table 10.1).



Scheme 10.1 Synthesis of 6-carbamoyl-2-alkyl-9-(phenyl or benzyl)-9*H*-purines; Reagents and conditions: i, RNH_2, $PhNH_3^+Cl^-$, r.t., 3–4 h; ii, DBU, EtOH, r.t.; iii, Dione, CH_3CN, r.t.

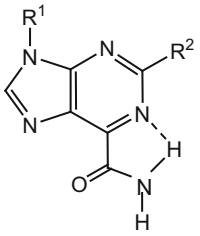
Table 10.1 Synthesis of purines **4a-d**

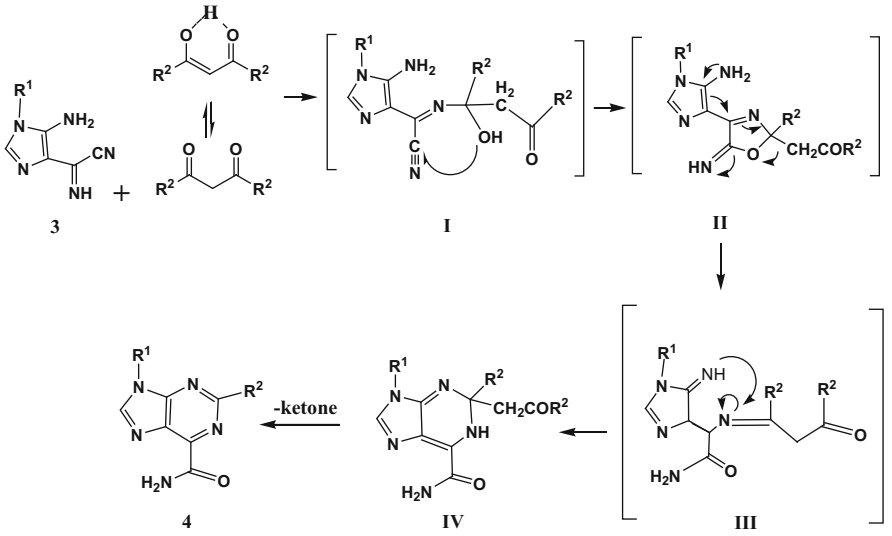
Entry	Product	R^1	R^2	Yield (%)
3a	**4a**	4-$(C_2H_5O)C_6H_4$-	CH_3-	72
3b	**4b**	3,4-$(CH_3O)_2C_6H_3CH_2$-	CH_3-	70
3c	**4c**	3,4-$(CH_3O)_2C_6H_3CH_2$-	4-$(CH_3)_2CH$-C_6H_4-	64
3d	**4d**	3,4-$(CH_3O)_2C_6H_3CH_2$-	3,4-$(CH_3O)_2C_6H_3$-	74

The spectroscopy results obtained on these compounds **3a-d** were satisfactory. The ^{1}H NMR spectra showed the presence of two broad singlets in the regions of 5.63–7.83 and 7.21–7.41 ppm due to the amine protons and a singlet at 7.21–11.05 ppm for the HC proton of the imidazole ring. The ^{13}C NMR spectra were fully consistent with the assigned structures. The infrared spectra confirmed the presence of the NH and C=N stretching vibrations within the region of 3,450–3,180, and 1,640–1,620 cm^{-1} respectively. The infrared spectra also showed a sharp absorption band at 2,300–2,200 cm^{-1} for the C≡N stretching vibration.

The purines **4a-d** were prepared by stirring a suspension of the corresponding 2-(5-amino-1-phenyl or benzyl)-4-(cyanoformimidoyl)-1*H*-imidazoles **3a-d** with a slight excess of dione in acetonitrile at room temperature (Scheme 10.1). The reactions were monitored by TLC (mixture of dry diethyl ether and chloroform 2:3) and reaction times varied between 20 and 24 h. Depending upon the solvent used for the reaction and the rate of precipitation, these purines can be isolated as solids in color from white to green. These were fully characterized by TLC, IR, ^{1}H NMR and mass spectroscopy. The infrared spectra of compounds **4a-d**

Scheme 10.2 The intra-molecular hydrogen bond in purine





Scheme 10.3 Proposed mechanism for the formation of purine **4**

confirmed the presence of the NH and C=N stretching vibrations within the region of 3,450–3,010, and 1,650–1,560 cm^{-1} respectively. The C=O of the amide group appeared in the region of 1,680–1,615 cm^{-1} as a strong band.

In the ^1H NMR spectra of the isolated compounds **4a-d**, the NH_2 protons appeared as two broad singlets in the range δ 6.29–8.56 ppm, because of combined intramolecular hydrogen bonding from an amide N-H to an N atom of the six-member pyrimidine ring and deshielding appears between H of NH_2 and N1 at purine (Scheme 10.2). The H-8 proton of the imidazoles ring was seen as a sharp singlet in the region of 8.18–9.09 ppm and the aromatic protons showed the expected patterns in the range of 7.01–7.70 ppm. The high resolution mass spectra gave a molecular ion peak at 298, 314, 433, 451 $(M + 1)^+$ which fit with the expected molecular weight of 297, 313, 432, 450 for the purines **4a-d**. The elemental analysis results of purines **4a-d** were satisfactory.

The proposed mechanism for formation of purine **4** is as follows**:** the first intermediate **I** was formed by the attack of imine to the carbonyl group of 1,3-dione thereby rearranging it to compound **II** and **III**. At the end purine **4** was formed with removal of the acetone from compound **IV** (Scheme 10.3).

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