



Synthesis of Novel 6-Cyano-9-(aryl)-9H-purine Derivatives Via Formamidine Intermediates

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Abstract: Novel 9-substituted cyanopurine derivatives (**4a-d**) were synthesized in three steps in high yield. Diaminomaleonitrile (**1**) reacted with triethyl orthoformate to afford (Z)-N-[2-amino-1,2-dicyanovinyl] formimide (**2**) which was converted to aryl-(Z)-N-[2-amino-1,2-dicyanovinyl] formamidines (**3a-d**) in the presence of a catalytic amount of anilinium chloride and aromatic amines in ethanol at room temperature under inert atmosphere (Argon). Furthermore, the reaction of (**3a-d**) with triethyl orthoformate afforded novel 6-cyano-9-(aryl)-9H-purine derivatives (**4a-d**) which can be used without further purification. All compounds have been fully characterized by spectroscopic data.

Keywords: Formimide, Aromatic amines, Formamidine, Triethyl orthoformate, 6-Cyanopurine

Introduction

Amidines are an important class of compounds which have proved to be intermediates in a number of biological processes¹⁻³. The chemistry and preparation of amidines have been reviewed by Shriner and Neumann⁴. Purine, purine nucleosides and their analogues have been extremely useful as anti-cancer agents⁵⁻⁸. Robins, in 1964, reviewed the anti-tumour activity of purine and purine nucleosides from a structure-activity stand-point. Subsequently several reviews on this subject have been published⁹⁻¹². 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) agents¹³. The chemotherapeutic uses of purines and purine analogues have prompted tremendous efforts towards their synthesis, both in academia and in the pharmaceutical industry. 6-cyanopurines are usually obtained by cyanide ion substitution of either 6-iodo¹⁴, 6-tosyl¹⁵,

6-methyle-sulfonyl^{16,17} and 6-trimethylammonio¹⁸ purine derivatives, or by dehydration of the 6-oximo derivatives with acetic anhydride¹⁹. The yields from these reactions are only moderate to poor. It has previously reported²⁰ that 6-cyanopurines can be obtained in good yields by reaction of 1-substituted-5-amino-4-(cyanoformimidoyl)-imidazoles with carboxylic acid anhydrides, but it is not always easy to isolate and handle these imidazole intermediates and we were interested in developing a simpler route to 6-cyanopurines. In continuation of our work on the synthesis of heterocyclic systems containing nitrogen²¹⁻²⁶, we described here the synthesis of new 6-cyano-9-(aryl)-9*H*-purine derivatives.

Experimental

All solvents purified and dried using established procedures. The ¹H NMR spectra were recorded on Bruker XL 500 (500 MHz) instruments, IR spectra on a shimadzu IR-470 spectrophotometer and mass spectra were recorded on a Kratos concept instrument. The C, H, N analyses were performed by the micro analytical service of the N.I.O.C. Research Institute of Petroleum Industry. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

General procedure for the preparation of the aryl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidines (3a-d)

The aromatic amine (1.22 mmol) was added to a suspension of formimidate (**2**) (0.20 g, 1.22 mmol) that previously was produced²⁷, in dry ethanol or ethylacetate (6 mL), which contained anilinium chloride (0.01 g). The mixture was stirred at room temperature under inert atmosphere (argon) for 9 hours. The reaction followed by TLC (8:2 ethylacetate / petroleumether) until all the formimidate (**2**) had disappeared and the amidine was isolated by filtration. The most cases, the product was pale green to white. The precipitate was washed with diethylether and air-dried to give the analytically pure product.

4-Ethoxyphenyl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine (3a)

(92.80%), Green, mp 148-150 °C; MS: *m/z* 255 (M)⁺; IR (KBr): 3450, 3350, 1470, 3100, 2950, 2210, 1630, 1590, 1375, 1465, 1280, 1240, 830 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.83 (br.s, 1H, NH), 7.70 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.87 (d, *J* = 8 Hz, 2H, Ar-H), 6.37 (br.d, 2H, NH₂), 4.00 (q, *J* = 13.90 Hz, 2H, CH₂), 3.35 (s, 1H, CH), 1.32 (t, *J* = 13.90 Hz, 3H, CH₃). Anal. Calcd. for C₁₃H₁₃N₅O: C, 61.17; H, 5.10; N, 27.39. Found: C, 61.20; H, 6.56; N, 8.15.

*1,4-Diaminophenyl-bis[(Z)-9*N*,9*N'*-(2-amino-1,2-dicyanovinyl)]formamidine (3b)*

(71.51%), Green, mp > 340 °C; MS: *m/z* 344 (M)⁺; IR (KBr): 3450, 3350, 3200, 2950, 2200, 1640, 1600, 1585, 1500, 1300, 1640, 810, 780 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.97 (br.s, 1H, NH), 7.73 (s, 4H, Ar-H), 6.55 (d, *J* = 8.69 Hz, 1H, CH), 6.32 (br.s, 2H, NH₂). Anal. Calcd. for C₁₆H₁₂N₂: C, 55.81; H, 3.48; N, 40.69. Found: C, 55.70; H, 3.50; N, 40.58.

2-Methoxybenzyl-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine (3c)

(65.22%), White, mp 147-150 °C; MS: *m/z* 344 (M)⁺; IR (KBr): 3500, 3400, 3100, 2950, 2200, 1620, 1550, 1480, 1300, 1465, 1340, 850, 830 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.97 (br.d, *J* = 4.90 Hz, 1H, NH), 7.71 (d, *J* = 4.04 Hz, 1H, CH), 7.27 (q, *J* = 7.52 Hz, 2H, Ar-H), 7.00 (d, *J* = 7.94 Hz, 1H, Ar-H), 6.91 (t, *J* = 7.43 Hz, 1H, Ar-H), 6.06 (s, 2H, NH₂), 4.47 (d, 2H, CH₂), 3.81 (s, 3H, OCH₃). Anal. Calcd. for C₁₃H₁₃N₅O: C, 61.17; H, 5.09; N, 27.45. Found: C, 61.20; H, 5.10; N, 27.39.

4-Hydroxy-(Z)-N-[2-amino-1,2-dicyanovinyl]formamidine (3d)

(94%), Pale green, mp 130 °C; MS: m/z 227 (M)⁺; IR (KBr): 3450, 3325, 3200, 3100, 2900, 2400, 1645, 1590, 1570, 1510, 1420, 1360, 1320, 960, 820, 750 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.72 (s, 1H, NH), 9.22 (s, 1H, CH), 7.64 (d, 2H, Ar-H), 6.72 (s, 2H, Ar-H), 6.28 (s, 2H, NH₂). Anal. Calcd. for C₁₁H₉N₅O: C, 58.14; H, 3.96; N, 30.83. Found: C, 57.98; H, 4.01; N, 30.39.

General procedure for the preparation of the 6-cyano-9-(aryl)-9H-purine (4a-d)

The mixture of formamidine (**3a-d**) (0.40 mmol) and triethyl orthoformate (3 mL, 6.33 mmol) were heated at reflux temperature for 6 hours until TLC (8:2, ethylacetate / petroleum ether) showed that all the formamidine (**3a-d**) had disappeared and the 9-substituted cyanopurines (**3a-d**) was isolated by filtration. The most cases the product was grey. The precipitate was washed with dry petroleum ether and air-dried. Obtained precipitates were recrystallized by ethanol to give the analytically pure product.

6-Cyano-9-(4-ethoxyphenyl)-9H-purine (4a)

(70%), Pale gray, mp 182-184 °C; MS : m/z 265 (M)⁺; IR (KBr): 3100, 2900, 2380, 1590, 1475, 1510, 1340, 1440, 1350 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.18 (s, 1H, H (Pyrimidine)), 9.09 (s, 1H, H (Imidazole)), 7.69 (d, J = 8.89 Hz, 2H, Ar-H), 7.10 (d, J = 8.92 Hz, 2H, Ar-H), 4.07 (q, J = 6.93 Hz, 2H, CH₂), 1.33 (t, J = 6.93 Hz, 3H, CH₃). Anal. Calcd. for C₁₄H₁₁N₅O: C, 63.39; H, 4.15; N, 26.41. Found: C, 62.40; H, 4.16; N, 26.36.

1,4-Phenylene-bis[9N,9N'-6-cyano-9H]purine (4b)

(71.1%), green, mp > 340 °C; MS : m/z 364.40 (M)⁺; IR (KBr): 3100, 2350, 1510, 1590, 1400, 1350 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.41 (s, 2H, H (Pyrimidine)), 9.20 (s, 2H, H (Imidazole)), 8.19 (s, 4H, Ar-H). Anal. Calcd. for C₁₈H₈N₁₀: C, 59.34; H, 2.23; N, 47.45. Found: C, 60.02; H, 2.23; N, 47.45.

6-Cyano-9-(2-methoxybenzyl)-9H-purine (4c)

(80.40%), Gray, mp 147-150 °C; MS : m/z 293 (M)⁺; IR (KBr): 3100, 2900, 2380, 1590, 1485, 1460, 1400, 1320, 1440, 1380 cm⁻¹; ¹H NMR (CDCl₃-d₁) δ 9.06 (s, 1H, H (Pyrimidine)), 8.35 (s, 1H, H (Imidazole)), 7.43 (d, J = 7.38 Hz, 1H, Ar-H), 7.35 (t, J = 7.94 Hz, 1H, Ar-H), 6.97 (t, J = 7.47 Hz, 1H, Ar-H), 6.92 (d, J = 8.28 Hz, 1H, Ar-H), 5.46 (s, 2H, CH₂), 3.87 (s, 3H, OCH₃). Anal. Calcd. for C₁₄H₁₁N₅O: C, 57.33; H, 3.75; N, 23.89. Found: C, 56.08; H, 3.70; N, 24.07.

6-Cyano-9-(4-hydroxy)-9H-purine (4d)

(75%), Brown, mp 208-210 °C; MS: m/z 237 (M)⁺; IR (KBr): 3200, 2380, 1500, 1460, 1400, 1320 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.00 (s, 1H, OH), 9.15 (s, 1H, H (Pyrimidine)), 9.11 (s, 1H, H (Imidazole)), 7.59 (d, J = 8.75 Hz, 2H, Ar-H), 6.95 (d, J = 8.79 Hz, 2H, Ar-H). Anal. Calcd. for C₁₂H₇N₅O: C, 60.75; H, 2.95; N, 29.53. Found: C, 59.90; H, 2.99; N, 29.95.

Results and Discussion

Formimidate (**2**) was prepared in high yield from diaminomaleonitrile (**1**) and triethyl orthoformate, according to a previously described procedure²⁷. Having obtained the imidate (**2**) in good yield it was then treated with aryl or benzylamine in a 1:1 or 1:2 molar ratio in dry ethanol in the presence of a catalytic amount of anilinium chloride and argon atmospheres. These compounds would be important intermediates

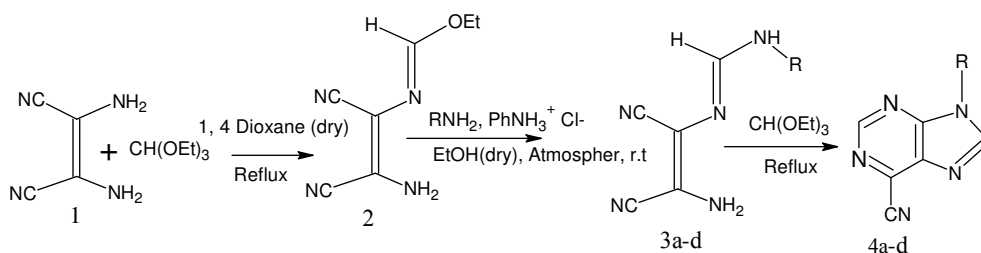
for the synthesis of a range of 9-aryl purines and 9-aryl-1,2-dihydropurines. We attempted to cyclise these amidines (**3a-d**) to obtain compounds (**4a-d**), via refluxing them with triethyl orthoformate (Scheme 1). The reactions followed by TLC (8:2 ethylacetate / petroleum ether) to all the starting material had been consumed. These compounds filtered, washed with petroleum ether and diethylether, recrystallized with ethanol. These were fully characterized by IR, ^1H -NMR, MS spectroscopy and elemental analysis.

The elemental analysis results of amidines (**3a-d**) were satisfactory. The infrared spectrum of amidines (**3a-d**) confirmed the presence of the NH and C=N stretching vibrations in 3480-3120 and 1600-1640 cm^{-1} respectively. The infrared spectrum also showed a sharp absorption band at 2220-2200 cm^{-1} for the CN stretching vibration. The mass spectra showed peaks at m/z 255 (**3a**), 344 (**3b**), 255 (**3c**) and 227 (**3d**) respectively.

The ^1H NMR spectra of compounds (**3b**) and (**3c**) had some interesting features. In compound (**3b**) ^1H NMR spectra has appeared NH proton as a broad singlet at $\delta=9.97$ ppm, aromatic ring protons as a singlet at $\delta=7.66$ -7.80 ppm, CH protons as a doublet at $\delta=6.55$ ppm and NH_2 protons as a singlet at $\delta=6.32$ ppm. In compound (**3c**) ^1H NMR spectra has appeared NH proton as a doublet at $\delta=7.96$ ppm, aromatic ring protons as $\delta=6.6$ -7.30 ppm, CH proton as a doublet at $\delta=7.71$ ppm, NH_2 protons as a singlet at $\delta=6.06$ ppm, two benzylic protons as a doublet at $\delta=4.47$ ppm and OCH_3 protons as a singlet at $\delta=3.81$ ppm.

The elemental analysis results of 9-substituted cyanopurines (**4a-d**) were satisfactory. The infrared spectrum of purines (**4a-d**) showed two strong absorptions for CN stretching vibrations in 2350-2380 cm^{-1} , C=N vibrations in 1510 cm^{-1} and C=C stretching vibration in 1400-1475 cm^{-1} . The mass spectrums showed a peak at m/z (%) 265 (**4a**), 364 (**4b**), 293 (**4c**), 237 (**4d**) respectively.

The ^1H NMR spectra of compounds (**4a**) and (**4b**) were satisfactory. In compound (**4a**) ^1H NMR spectra has appeared CH proton of the pyrimidine as a singlet at $\delta=9.18$ ppm, CH proton of the imidazole as a singlet at $\delta=9.09$ ppm, aromatic ring protons as two doublet at $\delta=7.1$ -7.69 ppm, CH_2 and CH_3 protons as a quartet at $\delta=4.05$ ppm and a triplet at $\delta=1.31$ ppm. In compound (**4b**) ^1H NMR spectra has appeared CH proton of the pyrimidine, CH proton of the imidazole, aromatic ring protons as a singlet at $\delta=9.41$, 9.2, 8.19 respectively.



a: R=4-ethoxy aniline, b: R=4 amino aniline, c: R=2-methoxy benzyl amine, d: R=4-hydroxy aniline

Scheme 1. Synthesis of novel 6-cyano-9(aryl)-9H-purine derivatives

Conclusion

In conclusion, a general and convenient synthesis of new 6-cyanopurine derivatives has been developed. The main advantages of these reactions are mild reaction conditions and high yields. The new compounds could be of interest in pharmacology and biology.

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