THE SYNTHESIS OF 6-C-SUBSTITUTED PURINES VIA α-(AMINOMETHYLENE)-6-PURINEACETONITRILE

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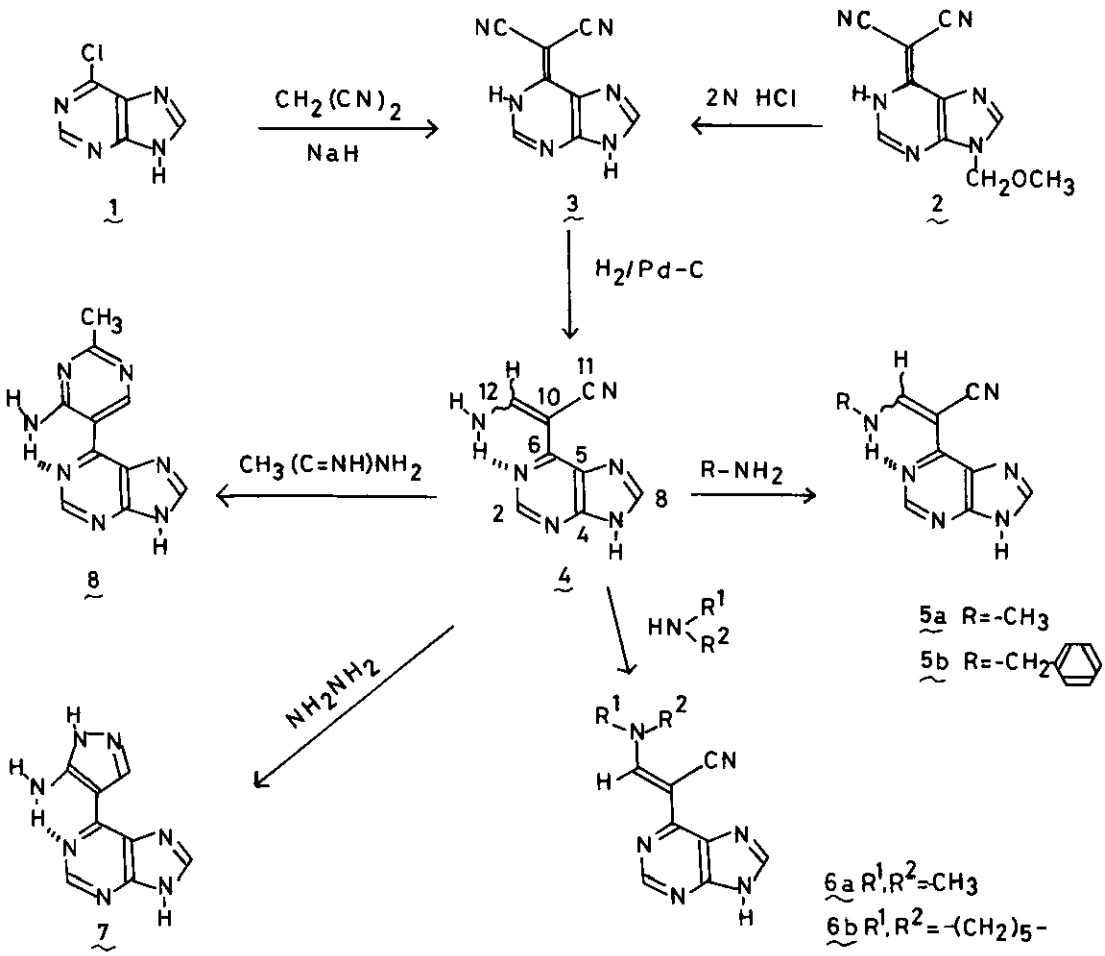
Abstract — 6-Purinemalononitrile (3), which was prepared by the substitution of 6-chloropurine (1) with malononitrile or deprotection of methoxymethyl group of (9-methoxymethyl-purin-6-yl)-malononitrile (2) with acid, has been catalytically hydrogenated to the α-(aminomethylene)-6-purineacetonitrile (4). Substitution of 4 with amines gave the corresponding alkylamines (5) and (6). Reaction of 4 with hydrazine and acetamidine hydrochloride gave pyrazole derivative (7) and pyrimidine derivative (8), respectively.

6-Substituted aminopurine derivatives exhibit a number of interesting biological activities.[2] Therefore, in recent years much attention has been focused on the 6-C-substituted purine derivative.

It is well known that cyanomethylene systems can be easily prepared in high yield by reaction of the sodium salt of an activated cyanomethylene with halogenated or methylsulfonated purine derivatives.[3] However, studies on the conversion of the cyano group of cyanomethylene compounds into aminomethylene functions have not been described because the solubility of starting materials is limited. As part of our studies on the synthesis of 6-C-substituted purine derivatives,[4] we describe here a new convenient synthetic method of α-(aminomethylene)-6-purineacetonitrile (4) via 6-purinemalononitrile (3) by means of catalytic hydrogenation in an N,N-dimethylformamide (DMF)-benzene solvent system, and synthesis of purine derivatives via 4.

The synthesis of α-(aminomethylene)-6-purineacetonitrile (4) and its derivatives is summarized in Scheme 1. Compound (3) was obtained in 70% yield by substitution of 6-chloropurine (1)[5] with malononitrile in the presence of sodium hydride in dimethyl sulfoxide (DMSO) or deprotection of methoxymethyl group of 6-purinemalononitrile (2)[4] with 2N hydrochloric acid. Hydrogenation of 3 over 5% Pd-C in DMF-ben-

Scheme 1



zene (1 : 1 v/v) under medium pressure (3.5-4.0 atm) gave 4 in 71% yield. When benzene-methanol (2 : 8 v/v) was used as solvent, 4 was obtained in 53% yield. The structure of 4 was established by ^{1}H-nmr and ^{13}C-nmr spectroscopies. The ^{1}H-nmr spectrum of 4 showed two sets of vinyl proton signals (δ 7.67 and δ 9.35) as a doublet of doublets which collapsed to a singlet with deuterium oxide. The ^{13}C-nmr spectrum of 4 also showed the presence of two nitrile signals at δ 117.8 ($^3J_{CN,H}$= 11.0 Hz, Z)[6] as the major and at δ 122.8 ($^3J_{CN,H}$=5.0 Hz, E) as the minor signal. Generally, it is known that geometrical isomers (E/Z) are present in enamino acetic acid derivatives.[7] Therefore, on the basis of these results the geometrical isomers of 4 exist in an enamino nitrile tautomeric equilibrium rather than the

imino nitrile equilibrium. The ratio of geometrical isomers (E/Z) in deuteriodimethyl sulfoxide (DMSO-d_6) is 16 : 84 by comparing the integration of vinyl protons of each isomer in the ^{1}H-nmr spectrum.

The substitution of **4** with methylamine and benzylamine while heating gave the corresponding *N-substituted enamines* (**5a** *and* **5b**) in 95% and in 76% yield, respectively. The ^{1}H-nmr spectrum of **5a** showed the presence of two sets of vinyl protons at δ 7.76 (E), and δ 9.25 (Z). The ratio of geometrical isomers (E/Z) in DMSO-d_6 was 30 : 70. Also, the ratio (E/Z) of **5b** in DMSO-d_6 was 33 : 67. Substitution of **4** with secondary amines gave **6a** in 96% yield and **6b** in 63% yield, respectively. The ^{1}H-nmr spectrum of **6a** showed vinyl proton at δ 9.29 (1H, s). The vinyl proton in **6b** was at δ 9.32 and was a singlet as well. These results indicate that the geometrical isomer of the N,N-dialkylenamine moiety was in Z form. Reaction of **4** with hydrazine or acetamidine hydrochloride gave the pyrazole (**7**) in 69% yield, and the pyrimidine (**8**) in 78% yield, respectively.

In conclusion, the present work demonstrates that catalytic hydrogenation of **3** to α-(aminomethylene)-6-purineacetonitrile (**4**) in DMF-benzene is highly chemoselective because the enamine moiety and purine ring are unaffected. Compound (**4**) is also shown to be a versatile compound for the preparation of 6-C-substituted purines having alkyl chains, pyrazole and pyrimidine rings.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (potassium bromide) were taken on a JASCO Model A-102 spectrophotometer. The uv spectra were measured using a *Hitachi Model EPS-3T spectrophotometer*. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on JEOL JNM-FX 100 spectrometer using tetramethylsilane as an internal standard. For the resonance signals the following abbreviations are used: s, singlet; d, doublet; m, multiplet; and dd, doublet of doublets. The mass spectra were measured by a JEOL JMS-D300 spectrometer.

6-Purinemalononitrile (3)

To a cold (0-5°C) stirred suspension of 60% sodium hydride (7.190 g, 0.18 mol) in dry DMSO (80 ml) was added dropwise a solution of malononitrile (13.50 g, 0.20 mol) in dry DMSO (36 ml) over a period of 1.5 h, and the solution was stirred for 1 h at room temperature under argon. After this time, a solution of **1** (6.20 g, 0.04 mol) in dry DMSO(40 ml) was added to the above solution and the solution was stirred for

24 h at 90°C. After cooling, the solution was diluted with water (80 ml) and acidified to pH 1 with conc. HCl. The precipitate was filtered and recrystallized from tetrahydrofuran-water to give **3** (5.180 g, 70%) as colorless needles, mp 280-284°C dec. Ir: 3220 (NH), 2220 (CN), 2200 (CN)cm^{-1}. Uv (methanol) λmax (ε): 211.5(11220), 235 (6165), 335 (24547)nm. ^{1}H-Nmr (DMSO-d_6) δ : 8.20 (1H, s, C_2H),8.27 (1H, s, C_8H), 13.40 (1H, broad s, NH). Ms m/z: 184 (M+),157. Anal. Calcd for $C_8H_4N_6$: C, 52.18; H, 2.19; N, 45.63. Found: C, 51.86; H, 2.10; N, 45.34.

Deprotection of methoxymethyl group of **2**

A solution of **2** (2.00 g) in 2N HCl (300 ml) was heated at 90°C for 45 min. The precipitate was filtered off, and the filtrate was allowed to stand overnight in an ice-bath. The precipitated crystals were filtered and recrystallized from tetrahydrofuran-water to give **3** (1.320 g, 82%) as colorless needles. This compound was identical (mp, ir, and ^{1}H-nmr) with an authentic sample described above.

9-(Aminomethylene)-6-purineacetonitrile (**4**)

A solution of **3** (2.00 g) in DMF-benzene (1:1 v/v, 240 ml) was hydrogenated over 5% Pd-C (3.6 g) at room temperature for 48 h and 3.5-4.0 atm pressure of hydrogen. The catalyst was filtered off, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel with DMF-methanol-dichloromethane (2:3:5 v/v/v) as eluent, and the solvent was evaporated in vacuo. The residue was recrystallized from DMF-ethanol to give **4** (1.435 g, 71%) as colorless needles, mp 220-223°C dec. Ir: 3340 (NH), 3160 (NH), 2200 (CN)cm^{-1}. Uv (methanol) λmax (ε): 230 (12590), 236(12300), 254 (6610), 266 (4070), 331 (22910), 340 (20900)nm. ^{1}H-Nmr (DMSO-d_6)δ: 7.67 (0.15H, dd, J=14 Hz, J=8 Hz, C=CH, Z), 7.78-8.27 (1.78H, m, NH, Z) 8.37 (0.85H, s, C_8H, Z), 8.43 (0.15H, s, C_8H, E), 8.56 (0.85H, s, C_2H, Z), 8.65 (0.15H, s, C_2H, E), 9.35 (0.85H, dd, J=14Hz, J=8 Hz, C=CH, Z), 10.87 (0.15H, m, NH, E), 13.35 (1H, broad s, NH). ^{13}C-Nmr (DMSO-d_6)δ: 75.5 (d, ^{2}J=3.7 Hz, C_{10}, E), 79.2 (d, ^{2}J=3.7 Hz, C_{10}, Z), 117.8 (d, ^{3}J=11.0 Hz, CN, Z), 122.8 (d, ^{3}J=5.0 Hz, CN, E), 126.3 (d, ^{3}J=12.2 Hz,C_5), 142.7 (d, ^{1}J=212.0 Hz, C_8, E), 143.2 (d, ^{1}J=213.0 Hz, C_8, Z), 151.3(m, C_4), 151.8 (d, ^{1}J=203.0 Hz, C_2, E), 152.4 (d, ^{1}J=201.0 Hz, C_2, Z), 152.5 (d.d, ^{3}J=12.0 Hz, ^{3}J=4 Hz, C_6, Z), 153.5 (d, ^{3}J=12.0 Hz, C_6, E), 157.0 (d, ^{1}J=168.0 Hz, C_{12}, E), 158.6 (d, ^{1}J=169.0 Hz, C_{12}, Z). Ms m/z: 186 (M+), 159. Anal. Calcd for $C_8H_6N_6.H_2O$: C, 47.06; H, 3.95; N, 41.16. Found: C, 47.34; H, 3.65: N, 41.35.

9-(Methylaminomethylene)-6-purineacetonitrile (**5a**)

A solution of **4** (0.300 g, 1.610 mmol) in 20% w/w ethanolic methylamine (8 ml, 64 mmol) was heated at 75°C for 1.5 h in a sealed tube. After cooling, the solvent was evaporated in vacuo. The residue was dissolved in methanol-CH_2Cl_2 (1:1 v/v, 30 ml), treated with a small amount of active carbon, and heated for 5 min. The active carbon was filtered off, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel(15 g) with methanol-CH_2Cl_2(1:1 v/v) as eluent, and the solvent was evaporated in vacuo. The residue was recrystallized from methanol-ethyl acetate (AcOEt) to give **5a** (0.306 g, 95%) as colorless needles, mp 205-208°C. Ir: 3400 (NH), 3176 (NH), 2196 (CN)cm^{-1}. Uv (methanol) λmax (ε):

237.5 (10232), 258 (6166), 342 (23988), 350 (21877)nm. ^{1}H-Nmr (DMSO-d_6)δ: 3.09-3.17 (3H, m, NMe), 7.76 (0.3H, d, J=13 Hz, C=CH, E), 8.19 (0.7H, m, NH, Z), 8.36 (1H, s, C_8H, Z, E), 8.54(0.7H, s, C_2H, Z), 8.61 (0.3H, s, C_2H, E), 9.25 (0.7H, d, J=15 Hz, C=CH, Z),11.09 (0.3H, broad s, NH, E). Ms m/z: 200 (M+). Anal. Calcd for $C_9H_8N_6$: C, 53.99; H, 4.03; N, 41.98. Found: C, 54.07; H, 4.03; N, 41.98.

α-(Benzylaminomethylene)-6-purineacetonitrile (5b)

A solution of **4** (0.300 g, 1.61 mmol) and benzylamine (0.517 g, 4.83 mmol) in ethanol (8 ml) was refluxed with stirring for 2.5 h. After cooling, the precipitate was filtered and recrystallized from methanol to give **5b** (0.338 g, 76%) as colorless needles, mp 225-227°C dec. Ir: 3360 (NH), 3172 (NH), 2196 (CN)cm^{-1}. Uv (methanol) λmax (ε): 234 (14125), 245 (13489), 257 (32359), 352 (30902)nm. ^{1}H-Nmr (DMSO-d_6) δ: 4.40-4.72 (2H, m, CH_2), 7.36 (5H, broad s, phenyl-H), 7.91 (0.33H, d, J=13 Hz, C=CH, E), 8.36 (1H, s, C_8H, E,Z), 8.55 (0.67H, s, C_2H, Z), 8.60 (0.33H, s, C_2H, E), 8.89 (0.67H, m, NH, Z), 9.36 (0.67H, d, J=12 Hz, C=CH, Z), 11.80 (0.33H, m, NH, E). Ms m/z: 276 (M+). Anal. Calcd for $C_{15}H_{12}N_6$: C, 65.20; H, 4.38; N, 30.42. Found: C, 65.44; H, 4.32; N, 30.12.

(Z)-α-(Dimethylaminomethylene)-6-purineacetonitrile (6a)

A solution of **4** (0.300 g, 1.61 mmol) in 20% w/w ethanolic dimethylamine (8 ml, 44 mmol) was heated at 75°C for 2 h in a sealed tube. After cooling, the solvent was evaporated in vacuo and the residue was dissolved in methanol-CH_2Cl_2 (1:1 v/v, 30 ml). The solution was heated with a small amount of active carbon for 5 min, filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (15 g) with methanol-CH_2Cl_2 (1:1 v/v) as eluent, and the solvent was evaporated in vacuo. The residue was recrystallized from methanol-AcOEt to give **6a** (0.332 g, 96%) as colorless prisms, mp 217-220°C dec. Ir: 3168 (NH), 2196 (CN)cm^{-1}. Uv (methanol) λmax (ε): 240 (10964), 264 (6918), 270 (6309), 340 (67608), 349 (23988)nm. ^{1}H-Nmr (DMSO-d_6)δ : 3.35 (6H, s, 2 x Me), 8.34 (1H, s, C_8H), 8.55 (1H, s, C_2H), 9.29 (1H, s, C=CH). Ms m/z: 214 (M+). Anal. Calcd for $C_{10}H_{10}N_6$: C, 56.06; H; 4.71; N, 39.23. Found: C, 56.35; H, 4.48; N, 39.50.

(Z)-α-(Piperidinomethylene)-6-purineacetonitrile (6b)

A solution of **4** (0.300 g, 1.61 mmol) and piperidine (0.411 g, 4.83 mmol) in ethanol (8 ml) was refluxed for 2 h. After cooling, the precipitate was filtered and recrystallized from methanol to give **6b** (0.258 g, 63%) as colorless needles, mp 208-210°C. Ir: 3180 (NH), 2196 (CN)cm^{-1}. Uv (methanol) λ max (ε): 242 (16218), 263 (9120), 271 (7943), 345 (36307), 350 (35481)nm. ^{1}H-Nmr (DMSO-d_6) δ : 1.69 (4H, m), 3.79 (4H, m), 8.37 (1H, s, C_8H), 8.56 (1H, s, C_2H), 9.32 (1H, s, C=CH). Ms m/z: 254 (M+). Anal. Calcd for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.05; H, 5.21; N,32.79.

6-(3-Amino-4-pyrazolyl)purine (7)

A solution of **4** (0.186 g, 0.001 mol) and hydrazine hydrate (0.250 g, 0.005 mol) in ethanol-DMF (1:1 v/v, 6 ml) was heated at 90°C for 5 h. After cooling, the solvent was evaporated in vacuo and the residue was recrystallized from DMF-hexane to give

7 (0.138 g, 69%) as colorless needles, mp 271-273°C dec. Ir: 3400 (NH), 3200 (NH) cm^{-1}. Uv (methanol) λmax (ε): 327 (13803), 258 (4265), 214 (14125), 203 (15488)nm. ^{1}H-Nmr (DMSO-d_6) δ : 6.69 (2H, broad s, NH_2), 8.43 (2H, s, C_8H and pyrazole-H), 8.68 (1H, s, C_2H), 13.12 (2H, broad s, 2 x NH). Ms m/z: 201.0742 (M+, Calcd: $C_8H_7N_7$: 201.0760).

6-(4-Amino-2-methyl-5-pyrimidinyl)purine (8)

To a solution of sodium n-propoxide in n-propyl alcohol [prepared from sodium (23 mg, 10.0 mgatom) and absolute n-propyl alcohol (4 ml)] was added acetamidine hydrochloride (0.378 g, 4.0 mmol) at room temperature under argon. The solution was stirred for 30 min at the same temperature. After this time a solution of 4 (0.186 g, 1.0 mmol) in dry DMF (6 ml) was added to the acetamidine solution, and the mixture was heated at 130°C for 6 h. After cooling, the solvent was evaporated in vacuo and the residue was dissolved in water (1 ml). The solution was adjusted to pH 7 with 2N HCl, and allowed to stand overnight. The precipitate was filtered and recrystallized from DMF-ether to give 8 (0.165 g, 78%) as yellow needles, mp 224-226°C dec. Ir: 3400 (NH), 3250 (NH)cm^{-1}. Uv (methanol) λmax (ε): 212 (27542), 254 (6025), 263 (7079), 270 (6760), 282 (6025), 335 (13182), 346 (12302)nm. ^{1}H-Nmr (DMSO-d_6) δ : 2.47 (3H, s, Me), 8.29 (1H, s, NH), 8.67 (1H, s, C_8H), 8.95 (1H, s, C_2H), 9.71 (1H, s, NH), 10.05 (1H, s, pyrimidine-H), 13.83 (1H, s, NH). Ms m/z: 227.0915 (M+, Calcd. $C_{10}H_9N_7$; 227.0925).

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