A CONVENIENT METHOD FOR THE SYNTHESIS OF 6-ENAMINOPURINE DERIVATIVES BY CATALYTIC HYDROGENATION OF 6-CYANOMETHYLENEPURINES

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Summary: 6-Cyanomethylenepurines have been catalytically hydrogenated to the corresponding α-(aminomethylene)purine-6-acetic acid derivatives in good yields using dimethylformamide-benzene as solvent over Pd-C under medium pressure.

Enamines are versatile starting materials and intermediates, which have been extensively utilized in heterocyclic synthesis.[1] Especially, an enamine function on heterocycles is important for the construction of fused heterocyclic compounds. To our knowledge, however, methods for the introduction of an enamine moiety into heterocycles such as pyridine, pyrimidine, quinoline, and purine have rarely been described in the literature.[2] Methods for the preparation of β-aminovinyl substituted heterocycles involve tedious steps and the applicability is restricted.[2e] In order to overcome these problems, a new synthetic method was required for the introduction of an enamine moiety into heterocycles.

Cyanomethylene systems can be easily prepared in high yield by heteroarylation of the sodium salt of an active methylene containing cyano groups with halogenated or methylsulfonated heterocycles,[3] yet no studies on the conversion of the cyano group into aminomethylene functionalities have been described.

As part of our study on the synthesis of 6-C-substituted purine derivatives,[4] we wish to report here a new convenient synthetic method of α-(aminomethylene)purine-6-acetic acid derivatives from 6-cyanomethylenepurine using catalytic hydrogenation in a dimethylformamide (DMF)-benzene solvent system.

6-Cyanomethylenepurines (2a-c) were prepared in good yield by the nucleophilic substitution of 6-chloro-9-(methoxymethyl)purine (1a, R=CH₂OMe) with the corresponding sodium salt of malononitrile, α-cyanoacetamide and ethyl cyanoacetate (4 equiv.) in DMF solution (Table I). 9-Unsubstituted 3a,c, on the other hand, were obtained from 2a,c by deprotection with 2N HCl at 90°C. But, when 2b was treated with 2N HCl, cyanoacetamide (3b) was not obtained. Therefore, 3b was prepared by the nucleophilic substitution 1b (R=THF), followed by

1a,b → 2a-d → 3a-c

$H_2C\begin{smallmatrix}R^1\\CN\end{smallmatrix}$ H_3O^+
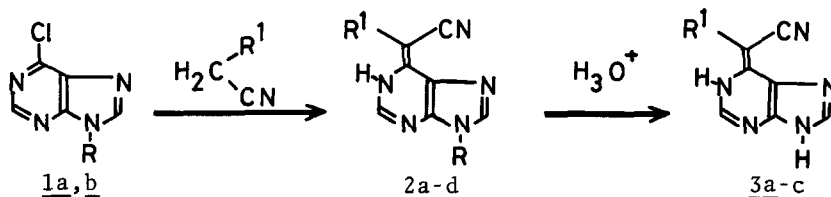
R=CH$_2$OMe(MOM),Tetrahydrofuranyl(THF)
R^1=CN,CONH$_2$,COOEt

Table I   Synthesis of 6-Cyanomethylenepurines (2 and 3)

Product[a]	R	R^1	Reaction Conditions		M.P.(°C dec.)[b]	Yield(%)
			Temp (°C)	h		
2a	MOM	CN	r.t	18	270-273	90
2b	MOM	CONH$_2$	r.t	15	199-201	82
2c	MOM	COOEt	70	20	241-256[c]	88
2d	THF	CONH$_2$	r.t	15	185-188	86
3a		CN	90	0.75	280-284	82
3b		CONH$_2$	r.t	3	225-228	99
3c		COOEt	90	0.5	238-242	92

a) Purification of the products was carried out by recrystallization. All the compounds gave satisfactory spectral data (IR, NMR) and elemental analyses.
b) Melting points are uncorrected.
c) Lit.,[3d] mp 240-261°C dec.

mild deprotection of 2d with 2N HCl.

When 2a was subjected to catalytic hydrogenation over 5% Pd-C in MeOH or DMF under medium pressure (3.5-4 atm) of hydrogen, 4a was obtained in low yield (10-30%).[5] Catalytic hydrogenation of 2a and 3a in DMF-benzene mixture (1:1) as solvent gave 4a and 4b, respectively, after purification by column chromatography on silica gel. It is known that geometrical isomers (E/Z) are present in the enaminoacetic acid derivatives.[6] However, the ^{1}H-NMR spectrum of 4a[7] showed two sets of vinyl proton signals (δ 7.71 and δ 9.28) as a doublet of doublets which collapsed to a singlet with D$_2$O. The ^{13}C-NMR spectrum of 4a showed the nitrile signal at δ 116.8 ($^3J_{CN,H}$=11.0 Hz, Z) as a major signal and at δ 121.2 ($^3J_{CN,H}$=4.9 Hz, E)[8] as a minor signal. Accordingly, on the basis of these results we conclude that it exists in an enamino nitrile tautomeric equilibrium (E/Z=14:86)[9] rather than the imino nitrile equilibrium.

Catalytic hydrogenation of the 6-cyanoamide (2d and 3b) over Pd-C in the presence of methanolic ammonia gave the corresponding 5a and 5b in good yields. The configuration of enamino amides (5a,b)[10] were assigned as the Z-form based

on their NMR spectra.

   On the other hand, catalytic hydrogenation of the ethyl 6-cyanoacetate (2c and 3c) afforded, after separation by column chromatography on florisil, the corresponding 6a[11] and 6b together with small amounts of 7a[12] and 7b, respectively. In the ^{1}H-NMR spectra of 6a, the two sets of vinylic proton signals were observed in the higher field (δ 7.94 and δ 8.11), which collapsed to a singlet with D_2O. But, the vinyl signal was not observed in the lower field. Chemical shifts of the vinyl protons and ^{1}H-NMR measurement under various temperatures suggested that the enamino esters (6a,b) exist in E-configurated isomeric structures (E-s-Z/E-s-E)[6b] up to 55°C.
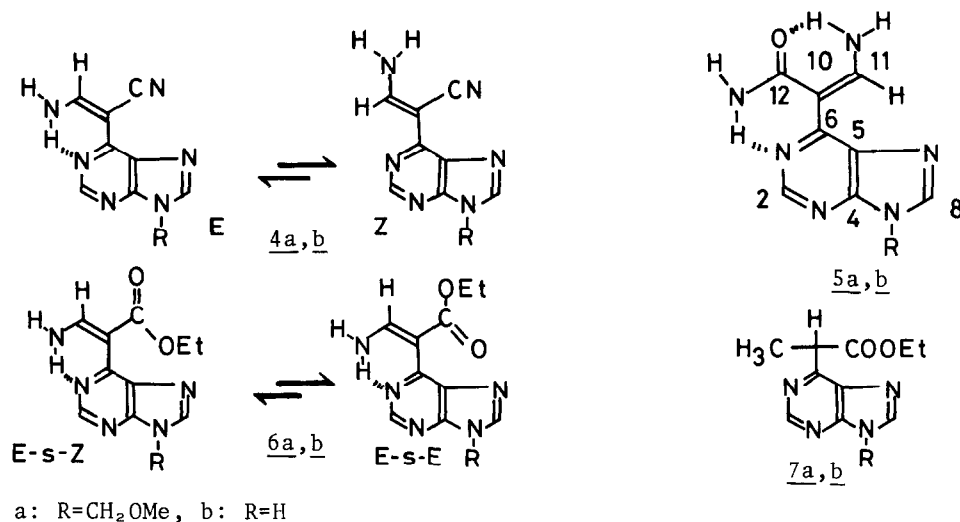

a: R=CH₂OMe, b: R=H

Table II Catalytic Hydrogenation of 6-Cyanomethylenepurines (2 and 3)[a]

Product[b]	Reaction Conditions		M.P. (°C)[d]	Isolated Yield (%)
	5% Pd-C (Wt%)[c]	h		
4a	30	40	201-203 dec.	71
4b	64	48	220-223 dec.	66
5a	59	48[f]	194-196 dec.	77
5b	75[e]	48[f]	205-207 dec.	65
6a	35	48	120-121	79
6b	75	48[f]	172-174	63
7a			55-56	15
7b			88-89	8

a) Reaction was carried out on a 3 mmol scale at room temperature under 3.5-4 atm pressure of H_2 in 100 ml of DMF-benzene (1:1 v/v). b) All the compounds gave satisfactory spectral data (IR,UV,NMR) and elemental analyses. c) Wt % of the catalyst to 2 and 3. d) Melting points are uncorrected. e) 10% Pd-C. f) In the presence of 5 ml sat.NH₃/MeOH as co-solvent.

Conditions of catalytic hydrogenation as well as yields of products (4-7) are summarized in Table II. From the results the present method has the following advantages: (1) Reaction proceeds under mild conditions; (2) The desired products are obtained from a short reaction sequence in satisfactory yields; (3) The catalytic hydrogenation is highly chemoselective because the enamine moiety and purine ring are unaffected. This method may also be useful for introduction of enamine moiety into other heterocyclic compounds.

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5) Catalytic hydrogenation in MeOH under ordinary pressure gave 4a in 8% yield.

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7) 4a: ^{1}H-NMR (DMSO-d_6) δ: 3.29 (3H, s, OMe), 5.57(2H, s, CH$_2$), 7.71 (0.14H, d.d, J=15.2 Hz, J=8.8 Hz, C=CH, E), 8.00-8.42 (1.70H, m, NH, Z), 8.56 (0.86H, s, C$_8$H, Z), 8.63 (1H, s, C$_2$H, Z and C$_8$H, E), 8.72 (0.14H, s, C$_2$H, E), 9.28(0.86H, d.d, J=15.8 Hz, J=8.3 Hz, C=CH, Z), 10.63 (0.14H, d, J=15.2 Hz, NH, E).[13]

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9) 4b: E/Z = 16:84 (in DMSO-d_6).

10) 5a: ^{1}H-NMR (DMSO-d_6) δ: 3.29 (3H, s, OMe), 5.57 (2H, s, CH$_2$), 6.99 (1H, b.s, CONH), 8.32 (1H, b.t, J=6.3 Hz, C=C-NH), 8.54 (1H, s, C$_8$H), 8.63 (1H, s, C$_2$H), 9.63 (1H, d.d, J=8.3 Hz, C=CH), 9.95-10.08 (2H, m, CONH and C=C-NH); ^{13}C-NMR δ: 95.8 (m, C-10), 126.2 (d, ^{3}J=11.0 Hz, C-5), 143 (d.t, ^{1}J=213.6 Hz, ^{3}J=3.7 Hz, C-8), 149.8 (m, C-4), 150.6 (d, ^{1}J=202.6 Hz, C-2), 156.3 (d.d, ^{3}J=10.9 Hz, ^{3}J=4.9 Hz, C-6), 159.6 (d, ^{1}J=166.0 Hz, C-11), 171.3 (d, ^{3}J=8.6 Hz, C-12).[14]

11) 6a: ^{1}H-NMR (CD$_3$COCD$_3$) δ: 1.17, 1.18 (3H, 2t, J=6.8 Hz, CH$_2$CH$_3$), 3.36 (3H, s, OMe), 4.17, 4.18 (2H, 2q, J=6.8 Hz, CH$_2$CH$_3$), 5.63 (1.14H, s, CH$_2$O), 5.65 (0.86H, s, CH$_2$O), 7.30 (0.57H, b.s, NH), 7.94 (0.43H, t, J=11.2 Hz, C=CH), 8.11 (1H, m, C=CH and NH), 8.33 (1H, s, C$_8$H), 8.68 (0.57H, s, C$_2$H), 8.76 (0.43H, s, C$_2$H).

12) a) 7a: ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7.3 Hz, CH$_2$CH$_3$), 1.56 (3H, d, J=7.3 Hz, CH-CH$_3$), 3.32 (3H, s, OMe), 4.06 (2H, q, J=7.3 Hz, CH$_2$CH$_3$), 4.50 (1H, q, J=7.3 Hz, CH-CH$_3$), 5.60 (2H, s, CH$_2$O), 8.66 (1H, s, C$_8$H), 8.88 (1H, s, C$_2$H); b) 7a was identical with ethyl 2-[9-(methoxymethyl)-9H-purin-6-yl]-propionate prepared from ethyl 9-(methoxymethyl)purine-6-acetate and CH$_3$I in NaOEt-EtOH.

13) The assignment of C$_2$H and C$_8$H were confirmed by comparing with 8-deuterated 4a.

14) These coupling constants were measured using deuterated (ND$_2$ and COND$_2$) 5a.

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