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Purines. V.[1] Reaction of 9-Phenyl-9*H*-purine-6-carbonitrile with Nucleophilic Reagents

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The reaction of 9-phenyl-9*H*-purine-6-carbonitrile (**1**) with nucleophilic reagents occurred by addition of the reagent across the C–N triple bond of the cyano group, and substitution of the cyano group was not observed.

Thus, the reactions with hydroxylamine, hydrazine, amines, Grignard reagents, and 98% sulfuric acid gave the corresponding amidoxime (**2**), amidorazone (**3**), amidines (**4**), ketones (**5**), and amide (**7**), respectively. Alcoholysis of **1** gave the ester (**6**) and **7** together with the ring fission product of the imidazole portion, alkyl 5-amino-6-anilino-4-pyrimidinecarboxylate (**8**).

Amides (**10**), the hydroxamic acid (**11**), and the hydrazide (**12**) were prepared from the methyl ester (**6a**).

Keywords——9-phenyl-9*H*-purine-6-carboxylic acid derivatives; addition reaction; Grignard reaction; ring fission; alcoholysis; nucleophilic reagent

We have reported that the reaction of 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carbonitrile (I) with a nucleophilic reagent can occur in two ways depending on the nature of the reagent used.[2] For example, the reaction of I with amines gave 7-alkylamino-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (substitution reaction), and the reaction with hydroxylamine afforded 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxamidoxime (addition reaction).[2]

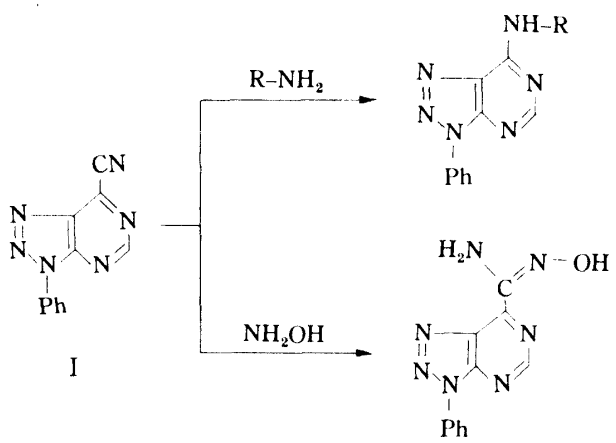


Chart 1

Since 9-phenyl-9*H*-purine-6-carbonitrile (**1**)[3] is considered to be a deaza analogue of I, it was expected that **1** might react with nucleophilic reagents in the same ways as I, *i.e.*, both substitution and addition reactions. Thus, we reacted **1** with several nucleophilic reagents, but found that only the addition reaction occurred. Some 9-phenyl-9*H*-purine-6-carboxylic acid derivatives were also prepared from the resulting methyl ester (**6a**).

In methanol, **1** reacted with hydroxylamine to give the amidoxime (**2**). The reactions with hydrazine, butylamine, and piperidine gave amidorazone (**3**) and the corresponding amidines (**4a** and **4b**), respectively.

When mixtures of **1** and Grignard reagents were refluxed in tetrahydrofuran (THF) and the resulting adducts were hydrolyzed, ketones (**5a**, **5b**, and **5c**) were formed, although the yields were poor (see Table I).

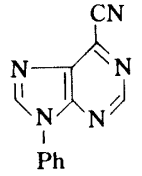
Alcoholysis by the introduction of dry hydrogen chloride gas into a solution of **1** in alcohols resulted in the formation of esters (**6a** and **6b**) and amide (**7**) together with pyrimidinecarboxylic acid esters (**8a** and **8b**) which were formed by ring fission of the imidazole portion of **1**. Many examples of ready ring fission of the imidazole portion of the 9*H*-purine ring system to form pyrimidine derivatives exist in the literature,[4-6] and the formation of **8** provides another. The pyrimidinecarboxylic acid esters (**8a** and **8b**) thus obtained were converted to the esters **6a** and **6b** by ring closure with ethyl orthoformate.

When a solution of **1** in 98% sulfuric acid was heated at 90°C for 5 min, sulfuric acid added across the C–N triple bond of the cyano group to form the adduct (**9**) which readily underwent hydrolysis to the amide (**7**) in excellent yield. Esterification of the amide (**7**) in alcohols in the presence of 98% sulfuric acid did not give the esters **6a** and **6b** but resulted in the formation of the pyrimidinecarboxylic acid esters (**8a** and **8b**).

TABLE I. Yields, Melting Points, and Elemental Analyses of Compounds **2** to **12**

No.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
2[a]	71	263—264[c]	$C_{12}H_{10}N_6O$	56.68 (56.49	3.96 3.89	33.06 32.90)
3[b]	79	215[c]	$C_{12}H_{11}N_7$	56.91 (56.82	4.38 4.39	38.72 38.56)
4a[a]	50	155—156	$C_{16}H_{18}N_6$	65.28 (65.09	6.16 6.21	28.55 28.52)
4b[a]	52	123—124	$C_{17}H_{18}N_6$	66.64 (66.41	5.92 5.91	27.43 27.33)
5a[b]	4	204—205	$C_{13}H_{10}N_4O \cdot 1/2\ H_2O$	63.15 (63.41	4.48 4.31	22.66 22.77)
5b[b]	16	170	$C_{14}H_{12}N_4O$	66.65 (66.74	4.79 4.88	22.21 22.25)
5c[a]	17	184—185	$C_{18}H_{12}N_4O$	71.99 (71.58	4.03 4.12	18.66 18.89)
6a[a]	26	176—177	$C_{13}H_{10}N_4O_2$	61.41 (61.23	3.96 4.00	22.04 22.30)
6b[a]	1	150—151	$C_{14}H_{12}N_4O_2$	62.68 (62.54	4.51 4.52	20.89 20.77)
7[a]	36[d], 57[e], 78[f]	233	$C_{12}H_9N_5O$	60.24 (60.00	3.79 3.83	29.28 29.16)
8a[b]	18[d], 57[g]	241—243	$C_{12}H_{12}N_4O_2 \cdot 1/3\ CH_3OH$	58.10 (58.37	5.27 5.13	21.98 22.24)
8b[b]	23[e], 40[g]	250—251	$C_{13}H_{14}N_4O_2$	60.45 (60.56	5.46 5.43	21.70 21.97)
10a[a]	51	182	$C_{16}H_{17}N_5O$	65.06 (64.87	5.80 5.80	23.72 23.67)
10b[a]	43	246—248	$C_{18}H_{13}N_5O$	68.56 (68.34	4.16 4.17	22.21 22.28)
11[a]	40	299—300[c]	$C_{12}H_9N_5O_2 \cdot HCl$	49.41 (49.62	3.46 3.58	24.01 24.13)
12[a]	80	283	$C_{12}H_{10}N_6O$	56.68 (56.63	3.96 3.95	33.06 32.68)

a) Colorless needles.
b) Yellow needles.
c) Decomposition.
d) Yield in methanolysis.
e) Yield in ethanolysis.
f) Yield in the reaction with 98% H_2SO_4.
g) Yield in the esterification of **7**.



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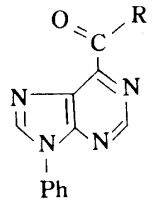
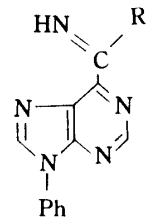


R

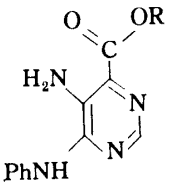
5a: Me
5b: Et
5c: Ph
6a: OMe
6b: OEt
7 : NH_2
10a: NHBu
10b: NHPh
11 : NHOH
12 : $NHNH_2$



R

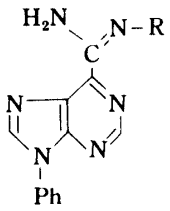
4b: N⟨⟩

9: OSO_3H



R

8a: Me
8b: Et



R

2: OH
3: NH_2
4a: Bu

Chart 2

TABLE II. IR and NMR Spectra of Compounds **2** to **12**

No.	IR ν_{max}^{KBr} cm^{-1}	NMR (in $CDCl_3$) ppm[a]			
		C^2–H^s	C^8–H^s	N^9–Ph(m)	Other
2[b]	3340 (NH or OH)	8.86	8.86	7.4—8.0	6.0 (br s, NH_2), 10.6 (br s, OH)
3	3360 (NH)				
4a	3350 (NH)	8.49	8.35	7.1—7.9	0.8—2.2 (m, $(CH_2)_2CH_3$), 3.94 (t, NCH_2CH_2, $J=7$ Hz) 7.1—7.9[c] (NH_2)
4b	3340 (NH)	8.50	8.40	7.1—7.9	1.7—4.4 (m, N⟨⟩), 8.9 (br s, NH)
5a	1700 (CO)	9.11	8.48	7.4—7.8	2.92 (s, $CO-CH_3$)
5b	1710 (CO)	9.03	8.41	7.3—7.8	1.30(t), 3.36 (q, $CO-CH_2CH_3$, $J=7$ Hz)
5c	1675 (CO)	9.06	8.37	7.3—8.2	7.3—8.2[c] ($CO-C_6H_5$)
6a[b]	1730 (CO)	9.10	9.05	7.3—8.0	4.02 (s, OCH_3)
6b[b]	1730 (CO)	9.08	8.46	7.3—7.9	1.51(t), 4.61 (q, OCH_2CH_3, $J=7$ Hz)
7[b]	1710 (CO) 3300, 3200 (NH)	9.05	8.98	7.4—8.6	7.4—8.6[c] (NH_2)
8a[b]	1700 (CO) 3300, 3200 (NH)	7.91	—	7.0—7.8	8.73 (br s, NH), 6.75 (br s, NH_2), 3.81 (s, OCH_3)
8b[b]	1700 (CO) 3280, 3190 (NH)	7.96	—	7.0—7.8	8.76 (br s, NH), 6.79 (br s, NH_2), 1.33(t), 4.30 (q, OC_2H_5, $J=7$ Hz)
10a	1690 (CO) 3310 (NH)	8.70	7.99	7.1—7.9	8.4 (br s, NH), 4.20 (t, NCH_2CH_2, $J=7$ Hz), 0.8—2.1 (m, $(CH_2)_2CH_3$)
10b[b]	1720 (CO) 3350 (NH)	9.16	9.13	7.1—8.1	10.8 (br s, NH), 7.1—8.1[c] ($N-C_6H_5$)
11	1710 (CO) 3320 (NH and OH)				
12[b]	1695 (CO) 3340 (NH)	8.51	8.15	7.0—8.0	5.8 (br s, NH_2), 9.5 (br s, NH)

a) br s, broad singlet, exchangeable with D_2O; m, multiplet; q, quartet; s, singlet; t, triplet.
b) NMR spectra in dimethyl sulfoxide-d_6.
c) Overlapping with N^9–C_6H_5.

The methyl ester (**6a**) was converted to *N*-butyl- (**10a**) and *N*-phenyl-amides (**10b**) by reaction with butylamine and aniline, respectively. Hydroxylamine and hydrazine also gave the hydroxamic acid (**11**) and hydrazide (**12**), respectively.

The structures of the compounds **2** to **12** thus obtained were suggested by their elemental analyses (Table I) and confirmed by analysis of their infrared (IR) absorption and nuclear magnetic resonance (NMR) spectra (Table II).

On the basis of these results, it appears that the reaction of **1** with nucleophilic reagents occurs by addition of the reagent across the C–N triple bond of the cyano group, and substitution of the cyano group does not occur. This is presumably due to the lower reactivity of the 6-position of **1** for nucleophilic reagents as compared with the carbon atom of the cyano group. As well as the addition reaction, ring fission of the imidazole portion is observed during the alcoholysis.

Experimental

All melting points are uncorrected. Yields and melting points of the compounds obtained are listed in Table I. IR spectra were recorded on a Jasco IRA-1 grating infrared spectrometer. NMR spectra were measured at 60 Mc and 23°C on a Hitachi R-24 high resolution NMR spectrometer using tetramethylsilane as an internal standard.

9-Phenyl-9*H*-purine-6-carboxamidoxime (**2**)——A mixture of 220 mg (1 mmol) of **1**, 280 mg (4 mmol) of $NH_2OH \cdot HCl$, and 330 mg (4 mmol) of AcONa in 10 ml of MeOH was refluxed for 45 min. The crystals formed by adding H_2O were collected, washed with H_2O, dried, and recrystallized from MeOH to give **2**.

9-Phenyl-9*H*-purine-6-carboxamidorazone (**3**)——A solution of 220 mg (1 mmol) of **1** and 156 mg (2.5 mmol) of 80% $NH_2NH_2 \cdot H_2O$ in 20 ml of EtOH was refluxed for 1 h. The resulting crystals were collected, washed with EtOH, dried, and recrystallized from MeOH to give **3**.

***N*-Butyl-9-phenyl-9*H*-purine-6-carboxamidine** (**4a**)——A solution of 220 mg (1 mmol) of **1** and 125 mg (2 mmol) of $BuNH_2$ in 3 ml of MeOH was refluxed for 1 h, then cooled. The crystals were collected, dried, and recrystallized from MeOH to give **4a**.

9-Phenyl-6-(1-piperidinecarboximidoyl)-9*H*-purine (**4b**)——A solution of 220 mg (1 mmol) of **1** and 170 mg (2 mmol) of piperidine in 3 ml of MeOH was refluxed for 4 h. The crystals, isolated as described in the preparation of **4a**, were recrystallized from petr. ether to give **4b**.

Methyl (**5a**), **Ethyl** (**5b**), **and Phenyl 9-Phenyl-9*H*-purin-6-yl Ketones** (**5c**)——Grignard reagents were prepared by the usual method from 2 mmol of alkyl halides (MeI, EtBr, and PhBr) and 50 mg of Mg in 5 ml of ether. This solution was gradually added to a stirred solution of 220 mg (1 mmol) of **1** in 10 ml of THF, and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and a solution of 1000 mg of NH_4Cl and 1 ml of 28% aqueous NH_3 in 5 ml of H_2O was added to the residue (adduct). The reaction mixture was extracted with $CHCl_3$ and dried over Na_2SO_4. The $CHCl_3$ extract was chromatographed on a column of Al_2O_3 using $CHCl_3$ as an eluent. The first fraction gave alkyl 9-phenyl-9*H*-purin-6-yl ketones (**5a**, **5b**, and **5c**) which were purified by recrystallization from MeOH.

Methanolysis of 1 (**Methyl 9-Phenyl-9*H*-purine-6-carboxylate** (**6a**), **9-Phenyl-9*H*-purine-6-carboxamide** (**7**), **and Methyl 5-Amino-6-anilino-4-pyrimidinecarboxylate** (**8a**))——Hydrogen chloride gas was introduced into a solution of 4.5 g (20 mmol) of **1** in 25 ml of MeOH until the solution was saturated. The mixture was stirred for 4.5 h and allowed to stand overnight at room temperature. The solvent was removed under reduced pressure, and the residue was neutralized with aqueous K_2CO_3. The reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4, and concentrated. The crystals were collected by suction and recrystallized from MeOH to give **8a**. The filtrate was chromatographed on a column of SiO_2 using $CHCl_3$ as an eluent. The first fraction gave **6a**, which was purified by recrystallization from benzene, and the second fraction gave **7**, which was recrystallized from MeOH.

Ethanolysis of 1 (**Ethyl 9-Phenyl-9*H*-purine-6-carboxylate** (**6b**), **7**, **and Ethyl 5-Amino-6-anilino-4-pyrimidinecarboxylate** (**8b**)——A solution of 4.5 g (20 mmol) of **1** in 25 ml of EtOH saturated with HCl gas was allowed to stand overnight at room temperature. Compounds **6b**, **7**, and **8b** were isolated using the method described in connection with the methanolysis of **1**.

Reaction of 1 with 98% H_2SO_4 (**Preparation of 7**)——A mixture of 442 mg (2 mmol) of **1** and 3.5 ml of 98% H_2SO_4 was heated at 90°C for 5 min, and the reaction mixture was poured onto 50 g of ice. The crystals separated by neutralization with K_2CO_3 were collected, washed with H_2O, and recrystallized from MeOH to give **7**.

Esterification of 7 (**Preparation of 8**)——i) A solution of 300 mg (1.25 mmol) of **7** and 0.5 ml of 98% H_2SO_4 in 8 ml of MeOH was refluxed for 3 h. MeOH was removed under reduced pressure, and the residue was poured into 10 ml of H_2O. The reaction mixture was neutralized with K_2CO_3, extracted with $CHCl_3$,

and dried over Na_2SO_4. Evaporation of $CHCl_3$ gave **8a**, which was recrystallized from benzene.

ii) A solution of 300 mg (1.25 mmol) of **7** and 0.5 ml of H_2SO_4 in 8 ml of EtOH was refluxed for 3 h. The crystals, isolated as described in connection with the preparation of **8a**, were recrystallized from petr. ether to give **8b**.

Ring Closure of 8 with Ethyl Orthoformate——A mixture of 1 mmol of **8**, 1 ml of $CH(OEt)_3$, and 1 ml of Ac_2O was refluxed for 3 h, and the solvent was removed under reduced pressure. The residue was neutralized with aqueous K_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and chromatographed on a column of SiO_2. The first fraction gave the ester (**6**).

Thus, the ring closure of **8a** and **8b** gave the esters **6a** in 67% yield (170 mg) and **6b** in 72% yield (193 mg), respectively.

***N*-Butyl- (10a) and *N*-Phenyl-9-phenyl-9*H*-purine-6-carboxamides (10b)**——i) A mixture of 254 mg (1 mmol) of **6a** and 146 mg (2 mmol) of $BuNH_2$ in 2 ml of MeOH was refluxed for 3.5 h, then the MeOH was removed under reduced pressure. The residue was extracted with $CHCl_3$ and dried over Na_2SO_4. The extract was chromatographed on a column of Al_2O_3 using $CHCl_3$ as an eluent. The first fraction gave **10a** which was recrystallized from benzene.

ii) A mixture of 153 mg (0.6 mmol) of **6a** and 1.5 g of aniline was heated at 170°C for 6 h. The reaction mixture was extracted with $CHCl_3$. The extract was washed with 2 N HCl and dried over Na_2SO_4. Evaporation of the $CHCl_3$ gave **10b**, which was recrystallized from MeOH.

9-Phenyl-9*H*-purine-6-carbohydroxamic Acid (11)——A mixture of 254 mg (1 mmol) of **6a**, 280 mg (4 mmol) of $NH_2OH \cdot HCl$, and 330 mg (4 mmol) of AcONa in 10 ml of MeOH was refluxed for 1 h. Twenty ml of H_2O was added to the reaction mixture, and the crystals were collected by suctio then dissolved in 2 N HCl to precipitate the hydrochloride of **11**, which was recrystallized from MeOH.

9-Phenyl-9*H*-purine-6-carbohydrazide (12)——A mixture of 254 mg (1 mmol) of **6a** and 125 mg (2 mmol) of 80% $H_2NNH_2 \cdot H_2O$ in 2 ml of MeOH was refluxed for 10 min. Methanol was removed under reduced pressure, and the crystals were recrystallized from MeOH to give **12**.

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References and Notes

1) Part IV: E. Hayashi, N. Shimada, Y. Matsuoka, and Y. Miwa, *Yakugaku Zasshi*, **99**, 207 (1979).
2) T. Higashino, T. Katori, S. Yoshida, and E. Hayashi, *Chem. Pharm. Bull.*, **28**, 255 (1980).
3) E. Hayashi, N. Shimada, and A. Miyashita, *Yakugaku Zasshi*, **96**, 1370 (1976).
4) B.R. Baker and H. Hewson, *J. Org. Chem.*, **22**, 959 (1957).
5) L.R. Lewis, F.H. Schneider, and R.K. Robins, *J. Org. Chem.*, **26**, 3837 (1961).
6) A.S. Jones, A.M. Mian, and R.T. Walker, *J. Chem. Soc. (C)*, **1966**, 692.