PURINES. IX.[1] REACTION OF 9-PHENYL-9H-PURINE-2-CARBONITRILES WITH GRIGNARD REAGENTS

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Abstract ——— The palladium-catalyzed cross-coupling reaction of 2- and 6-chloro-9-phenyl-9H-purines with potassium cyanide proceeded to give 9-phenyl-9H-purine-2- (3a-c) and -6-carbonitriles (4a-c). The conversion of the cyano group at the 2-position into the corresponding acyl groups was achieved by treatment of 3a,b with Grignard reagents.

We reported that 9-phenyl-9H-purine-2- (3a) and -6-carbonitriles (4a) were synthesized from 2- and 6-(methylsulfonyl)-9-phenyl-9H-purines and potassium cyanide (KCN)[2,3] and the selective addition of the nucleophiles to the cyano group at the 6-position of the 9H-purine took place.[4] It is well known that the cross-coupling reaction of aryl halides with KCN in the presence of a palladium complex was effective for preparation of aryl cyanides.[5]

In this paper, we describe the synthesis of 9-phenyl-9H-purine-2- (3a-c) and -6-carbonitriles (4a-c) by means of the cross-coupling reaction of 2- (1a-c) and 6-chloro-9-phenyl-9H-purines (2a-c) with KCN and the conversion of the cyano group at the 2-position into the corresponding acyl groups by the addition of Grignard reagents to the cyano group.

When a solution of 2-chloro-9-phenyl-9H-purine (1a), KCN, and bis(triphenylphosphino)palladium dichloride [$PdCl_2(PPh_3)_2$] in dimethylformamide (DMF) was refluxed for 2 h, 9-phenyl-9H-purine-2-carbonitrile (3a) was obtained in 53% yield. In order to confirm the generality of this reaction, several chloropurines such as 1b,c and 2a-c reacted with KCN in the presence of palladium catalyst under the same conditions, resulting in the formation of 9-phenyl-9H-purinecarbonitriles (3b,c and 4a-c).

Then we investigated the conversion of the cyano group at the 2-position into the

Dedicated to the late Professor Tetsuji Kametani.

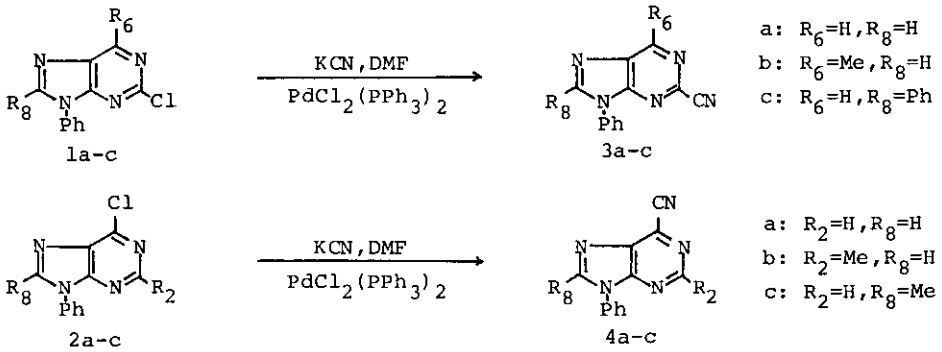

Table I. Yields, Ir Spectral Data, Melting Points, and Elemental Analyses for 3a-c and 4a-c

Compd	Yield (%)	Ir ν_{max}^{KBr} (cm^{-1})	mp (°C)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
3a	52	2240 (C≡N)	164-165[a]				
3b	58	2235 (C≡N)	190-195	$C_{13}H_9N_5$	66.37 (66.50)	3.86 (3.84)	29.77 (29.64)
3c	83	2235 (C≡N)	246-247	$C_{18}H_{11}N_5$	72.71 (73.13)	3.73 (3.79)	23.56 (23.22)
4a[c]	63		180-181[b]				
4b[c]	36		180-181	$C_{13}H_9N_5$	66.37 (66.38)	3.86 (3.85)	29.77 (29.61)
4c	43	2230 (C≡N)	217-218	$C_{13}H_9N_5$	66.37 (66.30)	3.86 (3.82)	29.77 (29.70)

a) Lit.[2] mp 164-165°C. b) Lit.[3] mp 181-182°C.
c) The absorption due to the cyano group was absent in the ir spectra.

acyl groups. It was already known that Grignard reagents selectively added to the cyano group at the 6-position of the 9H-purine ring, giving 6-acyl-9-phenyl-9H-purines. However, a little work[6] has been reported on introducing an acyl group into the 2-position of the 9H-purine ring.

The treatment of 3a with Grignard reagents such as methylmagnesium iodide and ethylmagnesium bromide in tetrahydrofuran (THF) at room temperature gave 2-acyl-9-phenyl-9H-purines (5a-d) by the addition of the Grignard reagents across the C-N triple bond at the 2-position, selectively. On the other hand, when we used phenylmagnesium bromide, the addition to both the 2-cyano group and the C^8,N^7-double bond occurred, followed by ready oxidation, to give 2-benzoyl-8,9-diphenyl-9H-purines (6a,b). Compound 6a was identified by the specimen synthesized by the reaction of 3c with phenylmagnesium bromide.

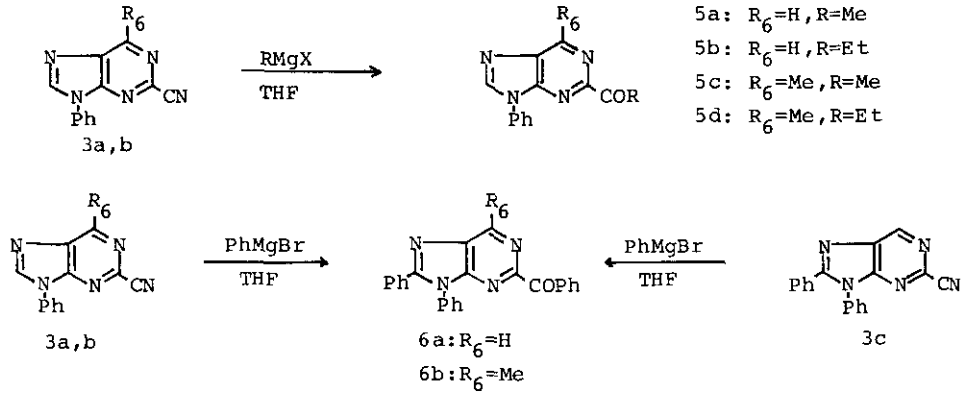

Table II. Yields, Ir Spectral Data, Melting Points, and Elemental Analyses for 5a-d and 6a,b

Compd	Yield (%)	Ir ν_{max}^{KBr} (cm^{-1})	mp(°C)	Formula	Analysis(%) Calcd(Found) C	H	N
5a	22	1704(C=O)	164-165[a]				
5b	39	1704(C=O)	158-160	$C_{14}H_{12}N_4O$	66.65 (66.90)	4.79 (4.83)	22.21 (21.91)
5c	51	1700(C=O)	174-175	$C_{14}H_{12}N_4O$	66.65 (66.65)	4.79 (4.81)	22.21 (21.95)
5d	49	1700(C=O)	149-150	$C_{15}H_{14}N_4O$	67.65 (67.53)	5.30 (5.25)	21.04 (20.96)
6a	43	1683(C=O)	244-245	$C_{24}H_{16}N_4O$	76.58 (76.34)	4.28 (4.26)	14.89 (14.82)
6b	30	1670(C=O)	209-210	$C_{25}H_{18}N_4O$	76.90 (76.71)	4.65 (4.72)	14.35 (14.10)

a) Lit.[6] mp 164-165°C.

The experimental results may be summarized as follows: i) 9-Phenyl-9H-purinecarbonitriles were easily synthesized from chloropurines by the cross-coupling reaction with KCN. ii) The conversion of the cyano group into the acyl group with Grignard reagents was a useful method for the synthesis of the 2-acyl derivatives of the 9H-purine.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measurred with a Jasco A-102 diffraction grating ir spectrophotometer. ^{1}H-Nmr spectra were taken at 60 MHz 23°C with a Hitachi R-24B high-resolution ^{1}H-nmr spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane as an internal standard.

2-Chloro-6-methyl-9-phenyl-9H-purine (1b) ——— A mixture of 5-amino-2,4-dichloro-6-methylpyrimidine[7] (19 g, 0.11 mol), aniline (10.2 g, 0.11 mol), concentrated HCl (4.5 ml), H_2O (290 ml), and EtOH (45 ml) was refluxed for 1 h. The precipitate, 5-amino-4-anilino-2-chloro-6-methylpyrimidine, was filtered off. Yield 23 g. A mixture of the crude 5-amino-4-anilino-2-chloro-6-methylpyrimidine (23 g, 0.098 mol), ethyl orthoformate (120 ml), and acetic anhydride (120 ml) was refluxed for 3 h. The resulting EtOH was removed under reduced pressure. The residue was diluted with H_2O. The mixture was made alkaline with anhyd. Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The crude product was purified by SiO_2 column chromatography with $CHCl_3$ and recrystallized from benzene to give 1b as colorless needles, mp 204°C. Yield 8 g (28%). Anal. Calcd for $C_{12}H_9ClN_4$: C, 58.90; H, 3.71; N, 22.90. Found: C, 58.68; H, 3.65; N; 22.77. ^{1}H-Nmr ($CDCl_3$) δ: 2.86 (3H, s, CH_3), 7.20-7.74 (5H, m, N^9-Ph), 8.20 (1H, s, C^8-H).

2-Chloro-8,9-diphenyl-9H-purine (1c) ——— A mixture of 5-amino-2,4-dichloropyrimidine[8] (18 g, 0.11 mol), aniline (10.2 g, 0.11 mol), concentrated HCl (4.5 ml), EtOH (45 ml), and H_2O (290 ml) was refluxed for 1 h. The precipitate, 5-amino-4-anilino-2-chloro-yrimidine, was filtered off. Yield 14.5 g. A mixture of the drude 5-amino-4-anilino-2-chloropyrimidine (2 g, 9.07 mmol), ethyl orthobenzoate (10 ml), and acetic anhydride (10 ml) was refluxed for 3 h. The same work-up of the reaction mixture as described for 1b gave 1c, colorless needles from benzene, mp 229-230°C. Yield 0.88 g (29%). Anal. Calcd for $C_{17}H_{11}ClN_4$: C, 66.65; H, 3.61; N, 18.26. Found: C, 66.50; H, 3.58; N, 18.19. ^{1}H-Nmr ($CDCl_3$) δ: 7.12-7.73 (10H, m, C^8-Ph and N^9-Ph), 9.00 (1H, s, C^6-H).

6-Chloro-2-methyl-9-phenyl-9H-purine (2b) ——— A mixture of 5-amino-4,6-dichloro-2-methylpyrimidine[9] (12 g, 0.067 mol), aniline (6.12 g, 0.067 mol), EtOH (25 ml), concentrated HCl (2.5 ml), and H_2O (170 ml) was refluxed for 1 h. The precipitate, 5-amino-4-anilino-6-chloro-2-methylpyrimidine, was filtered off. Yield 12 g. A mixture of the crude 5-amino-4-anilino-6-chloro-2-methylpyrimidine (12 g, 0.051 mol), ethyl orthoformate (60 ml), and acetic anhydride (60 ml) was refluxed for 3 h. The same work-up of the reaction mixture as described for 1b gave 2b, colorless needles from benzene, mp 178-180°C. Yield 11 g (67%). Anal. Calcd for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 59.10; H, 3.71; N, 22.93. ^{1}H-Nmr ($CDCl_3$) δ: 2.76 (3H, s, CH_3), 7.32-7.81 (5H, m, N^9-Ph), 8.24 (1H, s, C^8-H).

General Procedure for Cross-coupling of Chloropurines (1a-c and 2a-c) with KCN —

Table III. ^{1}H-Nmr Spectral Data for 3a-c, 4a-c, 5a-c and 6a,b

Compd	^{1}H-nmr ($CDCl_3$) δ ppm
3a	7.37-7.80(5H,m,N^9-Ph), 8.48(1H,s,C^8-H), 9.11(1H,s,C^6-H)
3b	2.90(3H,s,CH_3), 7.33-7.79(5H,m,N^9-Ph), 8.39(1H,s,C^8-H)
3c	7.08-7.68(10H,m,C^8-Ph and N^9-Ph), 9.09(1H,s,C^6-H)
4a	7.32-7.83(5H,m,N^9-Ph), 8.50(1H,s,C^8-H), 9.03(1H,s,C^2-H)
4b	2.84(3H,s,CH_3), 7.37-7.88(5H,m,N^9-Ph), 8.42(1H,s,C^8-H)
4c	2.64(3H,s,CH_3), 7.22-7.75(5H,m,N^9-Ph), 8.81(1H,s,C^2-H)
5a	2.77(3H,s,CH_3), 7.31-7.77(5H,m,N^9-Ph), 8.32(1H,s,C^8-H), 9.10(1H,s,C^6-H)
5b	1.27(3H,t,J=7.0Hz,$CH_2\underline{CH}_3$), 3.30(2H,q,J=7.0Hz,$\underline{CH}_2CH_3$), 7.32-7.98(5H,m,N^9-Ph), 8.49(1H,s,C^8-H), 9.28(1H,s,C^6-H)
5c	2.78(3H,s,C^6-CH_3 or $COCH_3$), 2.96(3H,s,C^6-CH_3 or $COCH_3$), 7.32-7.88(5H,m,N^9-Ph), 8.46(1H,s,C^8-H)
5d	1.26(3H,t,J=8.0Hz,$CH_2\underline{CH}_3$), 2.95(3H,s,CH_3), 3.28(2H,q, J=8.0Hz,$\underline{CH}_2CH_3$), 7.30-7.83(5H,m,N^9-Ph), 8.38(1H,s,C^8-H)
6a	7.20-7.61(13H,m,aromatic H), 7.89-8.13(2H,m,aromatic H), 9.26(1H,s,C^6-H)
6b	3.01(3H,s,CH_3), 7.21-7.85(13H,m,aromatic H), 7.94-8.24 (2H,m,aromatic H)

A mixture of a chloropurine (1 mmol), KCN (0.13 g, 2 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and DMF (5 ml) was refluxed for 2 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by SiO_2 column chromatography with benzene and recrystallized from benzene to give 3a-c and 4a-c.

General Procedure for the Reaction of 9-Phenyl-9H-purine-2-carbonitrile (3a,b) with Grignard Reagents ——— A solution of a 9-phenyl-9H-purine-2-carbonitrile (3a,b) (1 mmol) and a Grignard reagent (3 mmol) in THF (10 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was diluted with a mixture of 28% NH_4OH-NH_4Cl-H_2O (1:1:5) and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by SiO_2 column chromatography with benzene-$CHCl_3$ (1:1) and recrystallized from benzene to give 5a-d and 6a,b.

Reaction of 1c with Phenylmagnesium Bromide ——— A solution of 1c (0.15 g, 0.5 mmol) and PhMgBr (1 mmol) in THF (5 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was diluted with a mixture of 28% NH_4OH-NH_4Cl-H_2O (1:1:5) and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness. The residue was purified by SiO_2 column chromatography with benzene-$CHCl_3$ (1:1) and recrystallized from benzene to give 6a as colorless needles, mp 245-246°C. Anal. Calcd for $C_{24}H_{16}N_4O$: C, 76.58; H, 4.28; N, 14.89. Found: C, 76.25; H, 4.30; N, 14.68. ^{1}H-Nmr ($CDCl_3$) δ: 7.22-7.73 (13H, m, aromatic H), 7.93-8.16 (2H, m, aromatic H), 9.29 (1H, s, C^6-H). Ir ν_{max}^{KBr} cm^{-1}: 1683 (C=O).

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