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Triazolo[4,5-*d*]pyrimidines. IV.[1] The Grignard Reaction of 3-Substituted 3*H*-1,2,3-Triazolo[4,5-*d*]pyrimidines

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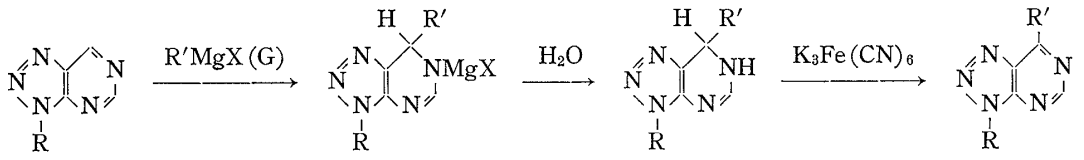
Grignard reactions of 3-methyl- (**1m**) and 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**1p**) resulted in the formation of 7-alkyl-6,7-dihydro-3-methyl- (**2m**) and 7-alkyl-6,7-dihydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**2p**) in moderate yields. These dihydro compounds **2m** and **2p** were converted into 7-alkyl-3-methyl- (**3m**) and 7-alkyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3p**), respectively, by oxidation with potassium ferricyanide.

Keywords——3-substituted 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines; Grignard reaction; 3-substituted 7-alkyl-6,7-dihydro-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines; oxidation; 3-substituted 7-alkyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines

Many reports on the Grignard reactions of π-deficient condensed pyrimidines have been published; for instance, quinoazoline (A) reacted with Grignard reagents to give 4-alkyl-3,4-dihydroquinazoline (A'),[3] pyrido[2,3-*d*]pyrimidine (B) gave 4-alkyl-3,4-dihydropyrido[2,3-*d*]-pyrimidine (B'),[4] 1-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine (C) afforded 4-alkyl-4,5-dihy-



1	–R	G	–R'	2	Yield (%)	3	Yield (%)
1m	$-CH_3$	G-1	CH_3	**2m**-1	30	**3m**-1	50
1m	$-CH_3$	G-1'	CD_3	**2m**-1'	34	**3m**-1'	46
1m	$-CH_3$	G-2	$-CH_2CH_3$	**2m**-2	53	**3m**-2	73
1m	$-CH_3$	G-2'	$-CD_2CD_3$	**2m**-2'	50	**3m**-2'	68
1m	$-CH_3$	G-2''	$-CH_2CD_3$	**2m**-2''	50	**3m**-2''	69
1m	$-CH_3$	G-3	$-CH(CH_3)_2$	**2m**-3	80	**3m**-3	80
1m	$-CH_3$	G-3'	$-CH(CD_3)_2$	**2m**-3'	81	**3m**-3'	77
1m	$-CH_3$	G-4	$-C(CH_3)_3$	**2m**-4	86	**3m**-4	86
1m	$-CH_3$	G-5	$-CH_2C_6H_5$	**2m**-5	62	**3m**-5	62
1m	$-CH_3$	G-6	$-C_6H_5$	**2m**-6	78	**3m**-6	78
1m	$-CH_3$	G-6'	$-C_6D_5$	**2m**-6'	80	**3m**-6'	73
1p	$-C_6H_5$	G-1	$-CH_3$	**2p**-1	86	**3p**-1	43
1p	$-C_6H_5$	G-2	$-CH_2CH_3$	**2p**-2	79	**3p**-2	44
1p	$-C_6H_5$	G-3	$-CH(CH_3)_2$	**2p**-3	83	**3p**-3	32
1p	$-C_6H_5$	G-5	$-CH_2C_6H_5$	**2p**-5	72	**3p**-5	44
1p	$-C_6H_5$	G-6	$-C_6H_5$	**2p**-6	71	**3p**-6	41

Chart 1

1) Part III: T. Higashino, T. Katori, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **27**, 2861 (1979).
2) Location: *a) 2-2-1 Oshika, Shizuoka*; *b) 1143 Nanpeidai, Narita.*
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dro-1*H*-pyrazolo[3,4-*d*]pyrimidines (C'),[5] and 9-phenyl-9*H*-purine (D) yielded 6-alkyl-1,6-dihydro-9-phenyl-9*H*-purines (D').[6] These results can be summarized as follows; the alkyl dihydro derivatives of condensed pyrimidines are formed by the addition of Grignard reagents across a double bond between the ring carbon and nitrogen atoms.

With the expectation that a similar reaction would take place, we reacted 3-substituted 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**1**) with Grignard reagents, and found that the expected reaction products, 3-substituted 7-alkyl-6,7-dihydro-1,2,3-triazolo[4,5-*d*]pyrimidines (**2**), were formed.

The Grignard reagents (G) used in this study were as follows: methyl- (G-1) and trideuteriomethyl-magnesium iodide (G-1'), ethyl-(G-2), pentadeuterioethyl- (G-2'), 2,2,2-trideuterioethyl- (G-2''), 1-methylethyl- (G-3) and 1-trideuteriomethyl-2,2,2-trideuterioethyl-magnesium bromide (G-3'), 1,1-dimethylethylmagnesium chloride (G-4), phenylmethyl- (G-5), phenyl- (G-6) and pentadeuteriophenyl-magnesium bromide (G-6').

Table I. EMM Values and IR Spectra of **2** and **3**

Compd.	mp (°C)	Composition	EMM: M^+ m/e		IR ν_{max}^{KBr} cm^{-1}
			Observed	Error[a]	=NH
2m-1	185—187[b]	$C_6H_9N_5$	151.0850	−0.7	3200
2m-1'	183—184[b]	$C_6H_6D_3N_5$	154.1038	−0.7	3200
2m-2	—[c]	$C_7H_{11}N_5$	165.1008	−0.6	3200[f]
2m-2'	—[c]	$C_7H_6D_5N_5$	170.1329	0.1	3200[f]
2m-2''	—[c]	$C_7H_8D_3N_5$	168.1180	−2.1	3200[f]
2m-3	—[c]	$C_8H_{13}N_5$	179.1163	−0.7	3200[f]
2m-3'	—[c]	$C_8H_7D_6N_5$	185.1553	0.6	3200[f]
2m-4	156—157[b]	$C_9H_{15}N_5$	193.1308	−1.9	3260
2m-5	—[c]	$C_{12}H_{13}N_5$	227.1156	−1.5	3200[f]
2m-6	—[c]	$C_{11}H_{11}N_5$	213.1004	−0.9	3200[f]
2m-6'	—[c]	$C_{11}H_6D_5N_5$	218.1309	−1.9	3200[f]
2p-1	187—188[b]	$C_{11}H_{11}N_5$	213.1015	0.1	3200
2p-2	129—130[b]	$C_{12}H_{13}N_5$	227.1166	−0.4	3200
2p-3	—[c]	$C_{13}H_{15}N_5$	241.1333	0.3	3210[f]
2p-5	125—126[b]	$C_{17}H_{15}N_5$	289.1345	1.5	3190
2p-6	152—154[b]	$C_{16}H_{13}N_5$	275.1195	2.1	3360
3m-1	80— 81[b]	$C_6H_7N_5$	149.0705	0.3	—
3m-1'	82— 83[b]	$C_6H_4D_3N_5$	152.0874	−1.5	—
3m-2	—[d]	$C_7H_9N_5$	163.0842	−1.5	—
3m-2'	—[d]	$C_7H_4D_5N_5$	168.1176	0.4	—
3m-2''	—[d]	$C_7H_6D_3N_5$	166.1046	0.0	—
3m-3	61— 62[b]	$C_8H_{11}N_5$	177.1011	−0.3	—
3m-3'	61— 62[b]	$C_8H_5D_6N_5$	183.1386	−0.4	—
3m-4	87— 88[b]	$C_9H_{13}N_5$	191.1182	1.0	—
3m-5	82— 83[b]	$C_{12}H_{11}N_5$	225.1008	−0.7	—
3m-6	141—142[b]	$C_{11}H_9N_5$	211.0858	−0.1	—
3m-6'	142—143[b]	$C_{11}H_4D_5N_5$	216.1188	1.5	—
3p-1	116—117[b]	$C_{11}H_9N_5$	211.0865	0.6	—
3p-2	44— 45[b]	$C_{12}H_{11}N_5$	225.1022	0.7	—
3p-3	72— 74[e]	$C_{13}H_{13}N_5$	239.1170	−0.2	—
3p-5	123—125[e]	$C_{17}H_{13}N_5$	287.1176	0.3	—
3p-6	127—128[e]	$C_{16}H_{11}N_5$	273.1013	−0.2	

a) Error from the theoretical value in millimass units.
b) Colorless needles from benzene or petr. ether.
c) Vicid oil.
d) Colorless liquid.
e) Slightly yellow needles from petr. ether.
f) Neat.

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TABLE II. NMR Data for **2** and **3**

Compd.	NMR (in $CDCl_3$) ppm[a]					
	N^3–CH_3[s]	N^3–C_6H_5[m]	C^5–H	N^6–H[bs]	C^7–H	C^7–R
2m-1[b]	3.75	—	7.11[d,c]	8.0	5.07[q]	1.41[d] (CH_3, J=7 Hz)
2m-1′[b]	3.75	—	7.10[d,c]	8.0	5.05[s]	—
2m-2	3.92	—	7.21[d,c]	6.8	5.10[t,d]	1.5—2.2[m], 0.97[t] (CH_2CH_3, J=8 Hz)
2m-2′	3.91	—	7.20[d,c]	7.0	5.08[s]	—
2m-2″	3.92	—	7.21[d,c]	6.6	5.12[t,d]	1.86[d,d] (CH_2CD_3)
2m-3	3.93	—	7.25[d,c]	6.7	4.99[d,d]	1.4—2.4[m], 0.95[d], 0.39[d] ($CH(CH_3)_2$, J=8 Hz)
2m-3′	3.90	—	7.25[d,c]	6.6	4.95[d,d]	2.0[d,d] ($CH(CD_3)_2$)
2m-4	3.90	—	7.30[d,c]	6.9	4.72[s]	0.99[s] ($C(CH_3)_3$)
2m-5	3.87	—	7.01[d,c]	6.0	5.30[dd,e]	3.38[dd,e], 2.95[dd,e], 7.1—7.5[m] ($CH_2C_6H_5$)
2m-6	3.78	—	—[f]	7.1	5.89[s]	7.2—7.4[m] (C_6H_5)
2m-6′	3.79	—	7.03[g]	7.0	5.89[s]	—
2p-1	—	7.2—8.1	7.84[d,h]	7.2	5.13[q]	1.51[d] (CH_3, J=7 Hz)
2p-2	—	6.9—8.1	7.80[d,h]	6.7	5.10[t,d]	1.7—2.2[m], 1.03[t] (CH_2CH_3, J=8 Hz)
2p-3	—	6.9—8.0	7.78[d,h]	7.1	4.94[d,d]	1.7—2.4[m], 0.94[d], 0.97[d] ($CH(CH_3)_2$), J=8 Hz)
2p-5	—	6.5—8.0	7.81[d,h]	6.0	5.33[dd,e]	3.37[dd,e], 3.05[dd,e], 7.2—7.4[m] ($CH_2C_6H_5$)
2p-6	—	6.7—8.2	7.77[d,h]	6.8	5.93[s]	7.2—7.3[m] (C_6H_5)
3m-1	4.37	—	9.03[s]	—	—	3.02[s] (CH_3)
3m-1′	4.32	—	8.99[s]	—	—	—
3m-2	4.35	—	9.03[s]	—	—	3.41[q], 1.53[t] (CH_2CH_3, J=8 Hz)
3m-2′	4.37	—	9.00[s]	—	—	—
3m-2″	4.39	—	9.08[s]	—	—	3.28[s] (CH_2CD_3)
3m-3	4.38	—	9.09[s]	—	—	3.90[m], 1.45[d] ($CH(CH_3)_2$, J=8 Hz)
3m-3′	4.37	—	9.04[s]	—	—	3.87[s] ($CH(CD_3)_2$)
3m-4	4.35	—	9.06[s]	—	—	1.65[s] ($C(CH_3)_3$)
3m-5	4.28	—	9.00[s]	—	—	4.63[s], 7.1—7.6[m] ($CH_2C_6H_5$)
3m-6	4.33	—	9.11[s]	—	—	7.4—8.9[m] (C_6H_5)
3m-6′	4.30	—	9.05[s]	—	—	—
3p-1	—	7.4—8.4	9.07[s]	—	—	3.07[s] (CH_3)
3p-2	—	7.4—8.4	9.06[s]	—	—	3.48[q], 1.57[t] (CH_2CH_3, J=8 Hz)
3p-3	—	7.4—8.4	9.12[s]	—	—	3.98[m], 1.60[d] ($CH(CH_3)_2$, J=8 Hz)
3p-5	—	6.7—8.3	9.04	—	—	4.67[s], 6.7—8.3[m,i] ($CH_2C_6H_5$)
3p-6	—	7.3—9.1	9.20	—	—	7.3—9.1[m,i] (C_6H_5)

a) bs, broad singlet and exchangeable with D_2O; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet: t, triplet.
b) In dimethyl sulfoxide-d_6 (DMSO-d_6).
c) $J_{5,6}$=3 Hz, changeable into a singlet on addition of D_2O.
d) J=4 Hz.
e) ABX pattern (C^7—$\overset{\overset{Ha}{|}}{\underset{\underset{Hx}{|}}{C}}$—$\overset{\overset{Hb}{|}}{}$$C_6H_5$, $J_{a,x}$=8 Hz, $J_{b,x}$=4 Hz, $J_{a,b}$=14 Hz).
f) Overlapping with C^7–C_6H_5.
g) $J_{5,6}$=2 Hz.
h) $J_{5,6}$=4 Hz, changeable into a singlet on addition of D_2O.
i) Overlapping with N^3–C_6H_5.

The molar ratio of 3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**1m**)[7] to alkyl halide used for the preparation of G was set at 1: 1.2. When a mixture of **1m** and G was refluxed for 3 hr in ether and the resulting adducts were hydrolyzed, 7-alkyl-6,7-dihydro-3-methyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**2m**) were formed in moderate yields (Chart 1). A similar reaction was also found to take place between 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**1p**)[8] and G in tetrahydrofuran (THF), affording the dihydro compounds (**2p**) in good yields.

The structures of the dihydro compounds (**2**) were established as follows. The *m/e* value of the molecular ion (M^+) in exact mass measurement (EMM) showed that **1** combined with G in a 1: 1 ratio, and the infrared absorption (IR) spectrum confirmed the presence of an =NH group (3200 cm^{-1}) in each dihydro compound (see Table I). The nuclear magnetic resonance (NMR) spectra of **1m** and **1p** showed the C^7-hydrogen signals at 9.67 and 9.68 ppm, respectively. However, in the dihydro compounds (**2**) the C^7-hydrogen signals lay between 4.72 and 5.93 ppm (Table II). These upfield shifts were compatible with saturation of the C^7,N^6-double bond.

The dihydro compounds (**2**) were converted into 3-substituted 7-alkyl-3*H*-1,2,3-triazolo-[4,5-*d*]pyrimidines (**3**) in moderate yields by oxidation with potassium ferricyanide.

The structures of **3** were suggested by their EMM values and confirmed by their NMR spectra, as shown in Tables I and II. Moreover, the compounds **3p-1** to **3p-6** were also obtained by the reaction of 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carbonitrile (**4p**) with the corresponding alkylmagnesium halides.[9]

The reactions mentioned above provide facile methods for the synthesis of 3-substituted 7-alkyl-6,7-dihydro- (**2**) and 3-substituted 7-alkyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3**).

Experimental[10]

IR spectra were recorded on a Jasco IRA-1 grating infrared spectrophotometer. NMR spectra were measured at 60 Mc and 23° on a Hitachi R-24 high resolution NMR spectrometer using tetramethylsilane as an internal standard. EMM values were determined with a JEOL JMS-01SG-2 mass spectrometer combined with a JEC-6 spectrum computer. Samples were vaporized in a direct inlet system.

Reaction of 1m with G——A solution of G prepared from alkyl halides (2.4 mmol) and Mg (73 mg, 3.0 mmol) in ether (5.0 ml) was added to a solution of **1m** (270 mg, 2.0 mmol) in ether (15.0 ml), and the mixture was refluxed for 3 hr. After cooling, aqueous NH_4Cl–NH_3 (a solution of NH_4Cl (2.0 g) and 28% NH_3 (1.0 ml) in H_2O (5.0 ml)) was added to the reaction mixture. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and chromatographed on a column of alumina, eluting with $CHCl_3$. The first eluate gave **2m**. The yields of **2m** are shown in Chart 1, while the melting points, EMM and IR data are listed in Table I, and NMR data in Table II.

Reaction of 1p with G——A solution of G prepared from alkyl halides (6.0 mmol) and Mg (182 mg, 7.5 mmol) in ether (10.0 ml) was added to a solution of **1p** (985 mg, 5.0 mmol) in THF (10.0 ml), and the reaction mixture was refluxed for 3 hr. The isolation was carried out as described for the reaction of **1m** with G. The first eluate gave **2p**. The yields of **2p** are shown in Chart 1, while the melting points, EMM and IR data are listed in Table I, and NMR data in Table II.

Oxidation of 2 with $K_3Fe(CN)_6$——A solution of $K_3Fe(CN)_6$ (658 mg, 2.0 mmol) in H_2O (2.0 ml) was added to a mixture of **2** (0.7 mmol), K_2CO_3 (276 mg), H_2O (2.0 ml), and benzene (5.0 ml), and the mixture was vigorously shaken for 2 hr at room temperature. The separated benzene layer was dried over Na_2SO_4 and chromatographed on a column of alumina, eluting with benzene. The first eluate gave **3**. The yields of **3** are shown in Chart 1, while the melting points and EMM values are listed in Table I, and NMR data in Table II.

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10) Melting points are uncorrected.