Grignard Reactions of 1-Phthalazine-, 2-Quinoxaline-, and 4-Cinnoline-carbonitrile

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(Received June 12, 1976)

The Grignard reactions of 1-phthalazine- (V-0), 2-quinoxaline(VI-0), and 4-cinnoline-carbonitrile (VII-0) were carried out. Grignard reagent used in this study was as follows; phenylmagnesium bromide, benzylmagnesium chloride, isopropylmagnesium bromide, ethylmagnesium bromide, and methylmagnesium iodide.

When a mixture of V-0 and Grignard reagent in tetrahydrofuran (THF) was refluxed for 3 hr, 1-alkylphthalazine (Va), 4-alkyl-3,4-dihydro-1-phthalazinecarbonitrile (Vc), 4-alkyl-1-phthalazinecarbonitrile (Vc'), 2-alkyl-1(2H)-phthalazinone (Vd), and 4-alkyl-3,4-dihydro-3-(1-phthalazinyl)-1-phthalazinecarbonitrile (Ve) were formed together with 1-benzoylphthalazine (Vb-1), 1,4-diethyl-phthalazine (Vf-4), 1,2-dihydro-1,1,2-triethyl-phthalazine (Vg-4), and 3,4-dimethyl-3,4-dihydro-1-phthalazinecarbonitrile (Vh-5), although the yields of all products were small.

The reaction of VI-0 in THF carried out under the same conditions as V-0 gave 2-alkylquinoxaline (VIa), 2-acylquinoxaline (VI-b), 3-alkyl-3,4-dihydro-2-quinoxalinecarbonitrile (VIc), 3-alkyl-2-quinoxalinecarbonitrile (VIc'), and 1-alkyl-2(1H)-quinoxalinone (VIId) together with 2,2':3',2''-terquinoxaline (VII), in very small yields.

The reaction of VII-0 with phenylmagnesium bromide and methylmagnesium iodide in benzene gave only d type of the compound (1-phenyl- (VIIId-1), and 1-methyl-4(1H)-cinnolinone (VIIId-5)), and did not isolate other type of the compound.

These, a, b, and c type of the compounds were expected reaction products, and other, c', d, e, f, g, and h type of the compounds were unexpected products. Especially, e type of the compound was the product peculiar to the Grignard reaction of V-0, and d type of the compound was characteristic product of the Grignard reactions of the cyanobenzodiazines except 4-quinazolinecarbonitrile (IV-0) giving only a type of the compound.

The possible mechanisms of the formations of a, b, c, c', d, and e type of the compounds were proposed.

Keywords—phthalazinecarbonitrile; quinoxalinecarbonitrile; cinnolinecarbonitrile; Grignard reaction; mechanism

Many of the investigations on the Grignard reaction of π -deficient heterocycles having cyano group have been published; 4-quinolinecarbonitrile (I-0) reacted with Grignard reagent to give 4-alkylquinoline (Ia) and 4-acylquinoline (Ib),²⁾ 3-quinolinecarbonitrile (II-0) gave 4-alkyl-1,4-dihydro-3-quinolinecarbonitrile (IIc),³⁾ 4-isoquinolinecarbonitrile (III-0) afforded 1-alkyl-1,2-dihydro-4-isoquinolinecarbonitrile (IIIc),⁴⁾ 4-quinazolinecarbonitrile (IV-0) yielded 4-alkylquinazoline (IVa).⁵⁾ These results are summarized as follows; cyano group is replaced by Grignard reagent with alkyl group (substitution), cyano group is converted into acyl group by the attack of Grignard reagent at the carbon atom of cyano group (acyl formation), and alkyl-cyano-dihydroheterocycles are formed by 1,2- or 1,4-addition of Grignard reagent to the ring carbon and nitrogen atoms (addition).

1) Location: 2-2-1, Oshika, Shizuoka-shi.

2) P. Rabe and R. Pasternack, *Ber.*, **46**, 1030 (1913).

3) M. Natsume and I. Utsunomiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 1595 (1972).

4) a) K. Matsumori, A. Ide, and H. Watanabe, *Nippon Kagaku Zasshi*, **92**, 80 (1971); b) M. Natsume and M. Wada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1589 (1972).

5) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **10**, 1043 (1962).

Chart 1

Chart 2

With expectation that similar reactions would take place, we carried out the reactions of 1-phthalazine-(V-0),⁶⁾ 2-quinoxaline- (VI-0),⁷⁾ and 4-cinnoline-carbonitrile (VII-0)⁸⁾ with Grignard reagent, and found that the expected reaction products have been formed together with unexpected products.

6) A. Hirsch and D.G. Orphanos, *Can. J. Chem.*, **44**, 1552 (1966).

7) E. Hayashi, C. Iijima, and Y. Nagasawa, *Yakugaku Zasshi*, **84**, 163 (1964).

8) E. Hayashi, Y. Akahori, and T. Watanabe, *Yakugaku Zasshi*, **87**, 1115 (1967).

TABLE I. Reaction of V-0 with R-MgX in THF

Starting material		Product									Recovery
R-MgX -R	V-0	Va (%)	Vb (%)	Vc (%)	Vc' (%)	Vd (%)	Ve (%)	Vf (%)	Vg (%)	Vh (%)	V-0 (%)
-C ₆ H ₅	V-0		Vb-1 1.6	Vc-1 22.2	Vc'-1 8.2		Ve-1 2.4				V-0 5.0
-CH ₂ C ₆ H ₅	V-0	Va-2 4.5		Vc-2 17.2	Vc'-2 2.5		Ve-2 2.9				V-0 7.0
-CH(CH ₃) ₂	V-0	Va-3 1.6		Vc-3 9.8		Vd-3 5.0					V-0 2.6
-C ₂ H ₅	V-0	Va-4 1.8		Vc-4 15.2		Vd-4 5.0		Vf-4 1.5	Vg-4 4.7		V-0 4.0
-CH ₃	V-0			Vc-5 46.4	Vc'-5 1.7	Vd-5 1.1	Ve-5 1.2			Vh-5 1.7	

TABLE II. IR and Mass Spectra of Va to h, and X

Compds.	Melting point (°C)	Formula	Analysis (%)			Mass spectra <i>m/e</i> : (M ⁺)		IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹ :		
			Calcd. (Found)			Calcd.	Obsd.	>NH	-CN	>C=O
			C	H	N					
Va-3 ^{a)}	159—160 ^{b)}	C ₁₇ H ₁₅ O ₇ N ₅	50.87 (50.64)	3.77 (3.77)	17.45 (17.21)					
Vc-1 ^{c)}	104—105	C ₁₅ H ₁₁ N ₃	77.23 (77.10)	4.75 (4.96)	18.02 (17.95)			3315	2210	
Vc-2 ^{d)}	114—115	C ₁₆ H ₁₃ N ₃	77.71 (77.58)	5.30 (5.25)	16.99 (16.89)			3320	2210	
Vc-3 ^{a)}	—	C ₁₂ H ₁₃ N ₃	72.33	6.57	21.09	199	199	3350 ^{e)}	2215 ^{e)}	
Vc-4 ^{a)}	—	C ₁₁ H ₁₁ N ₃	71.33	5.99	22.69	185	185	3330 ^{e)}	2210 ^{e)}	
Vc-5 ^{f)}	99—100	C ₁₀ H ₉ N ₃	70.15 (70.07)	5.30 (5.16)	24.55 (24.13)			3340	2215	
Vc'-2 ^{g)}	186—187	C ₁₆ H ₁₁ N ₃	78.35 (78.58)	4.52 (4.55)	17.13 (17.14)				2230	
Vc'-3 ^{h)}	145—146	C ₁₂ H ₁₁ N ₃	73.07 (72.66)	5.62 (5.61)	21.31 (21.18)				2230	
Vc'-4 ^{d)}	130	C ₁₁ H ₉ N ₃	72.11 (71.90)	4.95 (4.97)	22.94 (22.90)				2230	
Vd-3 ^{a)}	—	C ₁₁ H ₁₂ ON ₂	70.18	6.43	14.88	188	188			1650 ^{e)}
Vd-4 ^{d)}	56	C ₁₀ H ₁₀ ON ₂	68.95	5.79	16.08	174	174			1650
Ve-2 ^{c)}	174—175	C ₂₄ H ₁₇ N ₅	76.78 (76.76)	4.56 (4.51)	18.66 (18.70)				2220	
Vg-4 ^{a)}	—	C ₁₄ H ₂₀ N ₂	77.73	9.32	12.95	216.1628	216.1567 ^{d)}			
Vh-5 ^{f)}	93—94	C ₁₁ H ₁₁ N ₃	71.33 (71.38)	5.99 (5.93)	22.69 (22.26)				2210	
X ^{a)}	—	C ₁₂ H ₁₅ N ₂ Cl	64.71	6.79	12.58	222	222			

a) oil b) picrate c) yellow needles d) colorless needles e) in neat f) slightly yellow needles g) colorless plates
h) yellow prisms i) exact mass measurement

Grignard reagent used in this study was as follows; phenylmagnesium bromide, benzylmagnesium chloride, isopropylmagnesium bromide, ethylmagnesium bromide, and methylmagnesium iodide.

1-Phthalazinecarbonitrile (V-0)

The molar ratio between V-0 and alkyl halide, which was used for preparation of Grignard reagent, was set at 1:1.2. When a mixture of V-0 and Grignard reagent was refluxed for 3 hr in tetrahydrofuran (THF), the expected reaction products, 1-alkyl-(Va), 1-benzoyl-phthalazine (Vb-1), and 4-alkyl-3,4-dihydro-1-phthalazinecarbonitrile (Vc), were formed together

TABLE III. NMR Spectra of Vc to h, and X

Compds.	NMR (τ) in CDCl_3			
	H-5 to 8 ^m	H-4	NH ^{bs}	Other
Vc-1	2.5—2.8	4.36 ^s	3.0	2.5—2.8 ^{a),m} ($-\text{C}_6\text{H}_5$)
Vc-2	2.5—3.0	5.48 ^q	3.3	2.5—3.0 ^{a),m} ($-\text{C}_6\text{H}_5$), 7.32 ^q , 7.05 ^q ($\text{>CH}_x-\text{C}(\text{H}_a)(\text{H}_b)$, J_{a-b} : 13.0 cps, J_{a-x} : 7.5 cps, J_{b-x} : 6.0 cps)
Vc-3	2.4—2.8	5.65 ^d	3.0	8.12 ^m , 9.05 ^d , 9.17 ^d ($\text{>CH}_x-\text{CH}_a(\text{CH}_3)_2$, J_{a-x} : 6.0 cps, J : 8.0 cps)
Vc-4	2.4—2.8	5.33 ^m	3.1	8.30 ^m , 9.07 ^t ($\text{>CH}-\text{CH}_2-\text{CH}_3$, J : 8.0 cps)
Vc-5	2.4—2.8	5.32 ^q	2.9	8.54 ^d ($\text{>CH}-\text{CH}_3$, J : 6.1 cps)
Vc'-2	1.5—2.2			5.16 ^s ($-\text{CH}_2-$), 2.86 ^s ($-\text{C}_6\text{H}_5$)
Vc'-3	1.5—2.1			5.97 ^{sept} , 8.43 ^d ($-\text{CH}(\text{CH}_3)_2$, J : 8.0 cps)
Vc'-4	1.5—2.1			6.50 ^q , 8.45 ^t ($-\text{CH}_2\text{CH}_3$, J : 8.0 cps)
Vd-3	1.5—2.4	1.78 ^s		4.56 ^{sept} , 8.59 ^d ($\text{>N}-\text{CH}(\text{CH}_3)_2$, J : 8.0 cps)
Vd-4	1.4—2.5	1.82 ^s		5.69 ^q , 8.56 ^t ($\text{>N}-\text{CH}_2\text{CH}_3$, J : 8.0 cps)
Ve-2	2.0—3.0	3.24 ^q		0.68 ^s (H-4'), 1.12 ^m (H-8'), 2.0—3.0 ^{a),m} (H-5', 6', 7'), 6.57 ^q , 6.96 ^q ($\text{>CH}_x-\text{C}(\text{H}_a)(\text{H}_b)$, J_{a-b} : 14.0 cps, J_{a-x} : 9.0 cps, J_{b-x} : 5.0 cps)
Vf-4	1.8—2.4			6.73 ^q , 8.61 ^t ($2 \times -\text{CH}_2\text{CH}_3$, J : 8.0 cps)
Vg-4	2.6—3.2	2.96 ^s		6.75 ^q , 8.68 ^t ($\text{>N}-\text{CH}_2\text{CH}_3$, J : 8.0 cps), 8.10 ^q , 8.15 ^q , 9.21 ^t ($2 \times -\text{CH}_2\text{CH}_3$, J : 8.0 cps)
Vh-5	2.5—3.0	5.38 ^q		6.66 ^s ($\text{>N}-\text{CH}_3$), 8.73 ^d ($\text{>CH}-\text{CH}_3$, J : 6.1 cps)
X	2.3—3.0		4.27	8.48 ^q , 8.53 ^q , 9.44 ^t ($2 \times -\text{CH}_2\text{CH}_3$, J : 8.0 cps)

a) overlapping with aromatic H

bs: broad singlet and exchangeable with D_2O ; d: doublet; m: multiplet; q: quartet; s: singlet; sept: septet; t: triplet

VIa

VIa-2: R = $\text{CH}_2\text{C}_6\text{H}_5$
VIa-4: R = C_2H_5

VIb

VIb-1: R = C_6H_5
VIb-5: R = CH_3

VIc

VIc-2: R = $\text{CH}_2\text{C}_6\text{H}_5$
VIc-3: R = $\text{CH}(\text{CH}_3)_2$
VIc-4: R = C_2H_5

VIc'

VIc'-1: R = C_6H_5
VIc'-3: R = $\text{CH}(\text{CH}_3)_2$
VIc'-4: R = C_2H_5

VIId

VIId-2: R = $\text{CH}_2\text{C}_6\text{H}_5$
VIId-3: R = $\text{CH}(\text{CH}_3)_2$
VIId-4: R = C_2H_5
VIId-5: R = CH_3

VIIi

XI

Chart 3

with the unexpected products, 4-alkyl-1-phthalazinecarbonitrile (Vc'), 2-alkyl-1(2H)-phthalazinone (Vd), 4-alkyl-3,4-dihydro-3-(1-phthalazinyl)-1-phthalazinecarbonitrile (Ve), 1,4-diethyl- (V-f-4), 1,2-dihydro-1,1,2-triethylphthalazine (Vg-4), and 3,4-dimethyl-3,4-dihydro-1-phthalazinecarbonitrile (Vh-5), although the yield of each product was very small as summarized in Table I.

The identification of each of Va-2 (picrate), Va-4 (picrate), Vb-1, Vc'-1, Vc'-5, Vd-5, Ve-1, Ve-5, and Vf-4 (picrate) was, respectively, made by the mixed melting point test using

TABLE IV. Reaction of VI-0 with R-MgX in THF

Starting material		Product						Recovery
R-MgX -R	VI-0	VIa (%)	VIb (%)	VIc (%)	VIc' (%)	VI d (%)	VIi (%)	VI-0 (%)
-C ₆ H ₅	VI-0		VIb-1 8.1		VIc'-1 2.5		VIi 28.7	VI-0 1.4
-CH ₂ C ₆ H ₅	VI-0	VIa-2 14.1		VIc-2 12.3		VI d-2 5.9		
-CH(CH ₃) ₂	VI-0			VIc-3 2.0	VIc'-3 4.4	VI d-3 7.1		VI-0 26.2
-CH ₂ CH ₃	VI-0	VIa-4 3.5		VIc-4 2.5	VIc'-4 5.4	VI d-4 15.5		VI-0 5.2
-CH ₃	VI-0		VIb-5 4.5			VI d-5 1.2		VI-0 24.4

TABLE V. IR and Mass Spectra of VIc, d, and i

Compds.	Melting point (°C)	Formula	Analysis (%)			Mass spectra <i>m/e</i> : (M ⁺)		IR $\nu_{\text{max}}^{\text{KBr}}$ cm ⁻¹ :		
			Calcd. (Found)			Calcd.	Obsd.	>NH	-CN	>C=O
			C	H	N					
VIc-2 ^{a)}	179—181	C ₁₆ H ₁₃ N ₃	77.71 (77.69)	5.30 (5.18)	16.99 (16.89)			3290	2220	
VIc-3 ^{a)}	145—146	C ₁₂ H ₁₃ N ₃	72.33 (72.22)	6.57 (6.52)	21.09 (20.96)			3270	2220	
VIc-4 ^{b)}	130—131	C ₁₁ H ₁₁ N ₃	71.33 (71.85)	5.99 (5.90)	22.69 (22.90)			3280	2210	
VIc'-3 ^{c)}	107—108	C ₁₂ H ₁₁ N ₃	73.07 (72.85)	5.62 (5.65)	21.31 (21.16)				2230	
VI d-2 ^{c)}	122—123	C ₁₅ H ₁₂ ON ₂	76.25 (76.29)	5.12 (5.24)	11.86 (11.92)					1650
VI d-3 ^{d)}	—	C ₁₁ H ₁₂ ON ₂	70.18	6.43	14.88	188	188			1655 ^{e)}
VI d-4 ^{c)}	64—65	C ₁₀ H ₁₀ ON ₂	68.95 (68.99)	5.79 (5.91)	16.08 (16.11)					1660
VIi ^{f)}	above 300	C ₂₄ H ₁₄ N ₆	74.60	3.65	21.75	386.1282	386.1259 ^{g)}			

a) pale rose scaly crystals
g) exact mass measurement

e) reddish needles

c) colorless needles

d) oil

e) in neat;

f) yellow needles

the corresponding authentic specimen⁹⁻¹⁶⁾ prepared by each specific route. The structures of Va-3, Vc'-2 to Vc'-4, Ve-2, and Vh-5 were indicated by their elemental analyses or mass (Mass) spectra and confirmed by infrared (IR) and nuclear magnetic resonance (NMR) spectra shown in Table II and III. The adducts (Vc) were converted into the corresponding V-c' by the oxidation with potassium ferricyanide. Each of Vd-3 and Vd-4 was prepared by the reaction of 1(2*H*)-phthalazinone (VIII) with the corresponding alkyl halide in the presence of potassium carbonate. Assignment of Vg-4 was established by the following spectral data; *m/e* of the molecular ion peak (M⁺) in exact mass measurement corresponded to C₁₄H₂₀N₂ (calcd.: 216.1628, observed: 216.1567.), there were no characteristic absorption bands caused

9) E. Hayashi, E. Ôishi, T. Tezuka, and K. Ema, *Yakugaku Zasshi*, **88**, 1333 (1968).

10) E. Ôishi, *Yakugaku Zasshi*, **89**, 959 (1969).

11) A. Lieck, *Ber.*, **38**, 3918 (1905).

12) E. Hayashi and E. Ôishi, *Yakugaku Zasshi*, **86**, 576 (1966).

13) E. Hayashi, T. Higashino, and I. Watanabe, *Yakugaku Zasshi*, **93**, 409 (1973).

14) A. Albert and G.B. Barlin, *J. Chem. Soc.*, **1962**, 3129.

15) E. Ôishi, K. Ôsumi, and E. Hayashi, *Yakugaku Zasshi*, **94**, 672 (1974).

16) C.R. Warner, E.J. Walsh, and R.F. Smith, *J. Chem. Soc.*, **1962**, 1232.

TABLE VI. NMR Spectra of VIc, d, and i

Compds.	NMR (τ) in CDCl ₃			
	H-5 to 8 ^m	H-3	>NH ^{bs}	Other
VIc-2 ^a	2.2—3.5	5.4 ^m	3.2	7.18 ^d (>CH-CH ₂ -, <i>J</i> : 6.0 cps), 2.2—3.5 ^{b),m} (-C ₆ H ₅)
VI-c3	2.5—3.6	6.02 ^d (<i>J</i> : 6.0 cps)	6.0	7.89 ^m , 8.93 ^d , 9.04 ^d (>CH-CH(CH ₃) ₂ , <i>J</i> : 7.0 cps)
VIc-4	1.5—3.6	5.79 ^m	7.0	8.25 ^m , 8.97 ^m (>CH-CH ₂ -CH ₃)
VIc'-3	1.5—2.8			6.23 ^{sept} , 8.51 ^d , (-CH(CH ₃) ₂ , <i>J</i> : 7.0 cps)
VID-2	2.0—3.2	1.67 ^s		4.57 ^s (>N-CH ₂ -Ar), 2.0—3.2 ^{b),m} (-C ₆ H ₅)
VID-3	1.9—2.9	1.77 ^s		4.65 ^{sept} , 8.32 ^d (>N-CH(CH ₃) ₂ , <i>J</i> : 7.0 cps)
VID-4	1.9—2.8	1.72 ^s		5.68 ^q , 8.64 ^t (>N-CH ₂ CH ₃ , <i>J</i> : 7.0 cps)
VIi ^c	0.7—2.5 ^d			

^a) in (CD₃)₂SO ^b) overlapping with aromatic H ^c) in CF₃COOD ^d) fourteen aromatic H

bs: broad singlet and exchangeable with D₂O; d: doublet; m: multiplet; q: quartet; s: singlet; sept: septet; t: triplet

by cyano and imino groups in its IR spectrum, and the singlet peak (τ : 2.96) caused by the hydrogen at the 4-position and the peaks caused by three ethyl groups were recognized in its NMR spectrum. The splitting shape and chemical shift (τ : 8.10, quartet, 8.15, quartet, 2 $\times$ -CH₂-; 9.21, triplet, 2 $\times$ -CH₃, *J*: 8.0 cps) caused by two of three ethyl groups were similar to those of geminal ethyl groups of 4-chloro-1,1-diethyl-1,2-dihydrophthalazine (X) (τ : 8.48, quartet, 8.53, quartet, 2 $\times$ -CH₂-; 9.44, triplet, 2 $\times$ -CH₃, *J*: 8.0 cps) prepared from the Grignard reaction of 1,4-dichlorophthalazine (IX) with ethylmagnesium bromide.

2-Quinoxalinecarbonitrile (VI-0)

The molar ratio between VI-0 and alkyl halide, which was used for the preparation of Grignard reagent, was set at 1:1.2. When a mixture of VI-0 and Grignard reagent in THF was treated under the same conditions as the Grignard reaction of V-0, the expected product, 2-alkyl- (VIa), 2-acyl-quinoxaline (VIb), 3-alkyl-3,4-dihydro-2-quinoxalinecarbonitrile (VIc), were formed together with the unexpected products, 3-alkyl-2-quinoxalinecarbonitrile (VIc'), 1-alkyl-2(1*H*)-quinoxalinone (VID), and 2,2':3',2''-terquinoxaline (VI-i), although the yield of each products was very small, as shown in Table IV.

The identification of each of VIa-2 (picrate), VIa-4 (picrate), VIb-1, VIb-5, VIc'-1, VI-c'-4, and VI-d-5 was, respectively, made by the mixed melting point test using the corresponding specimen¹⁷⁻²³⁾ prepared by each specific route. The structures of VIc-2 to VIc-4, VIc'-3, VID-2, and VID-3 were indicated by the data of their elemental analyses or of *m/e* of M⁺ in Mass spectra, and confirmed by IR and NMR spectra shown in Table V and VI. The compound VID-4 was also identified by its synthesis obtained from 2(1*H*)-quinoxalinone (XI) and ethyl bromide in the presence of potassium carbonate. The structure of Vi was presumed through the following spectral data; *m/e* of M⁺ in exact mass measurement corresponded to C₂₄H₁₄N₆ (calcd.: 386.1282, observed: 386.1259.), there were no characteristic absorption bands caused by cyano and imino groups in its IR spectrum, and there were no other peaks except ones caused by fourteen aromatic

VIId
VIId-1: R = C₆H₅
VIId-5: R = CH₃

Chart 4

- 17) G.M. Bennet and G.H. Willis, *J. Chem. Soc.*, **1928**, 1966.
- 18) E. Hayashi and Y. Miura, *Yakugaku Zasshi*, **87**, 643 (1967).
- 19) H. Dahn and H. Moll, *Helv. Chim. Acta*, **49**, 2426 (1966).
- 20) G. Henseke and K.J. Böhner, *Ber.*, **91**, 1605 (1958).
- 21) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962).
- 22) E. Hayashi and T. Miyagishima, *Yakugaku Zasshi*, **87**, 1103 (1967).
- 23) G.W. Cheeseman, *J. Chem. Soc.*, **1955**, 1804.

TABLE VII. Reaction of VII-0 with R-MgX and C₆H₅-Li in Benzene

Starting material		Reaction condition		Product	
R-MgX	VII-0	Time (hr)	Temp.	VIIId	Yield (%)
C ₆ H ₅ -MgBr	VII-0	1	refluxing	VIIId-1	6.4
CH ₃ -MgI	VII-0	3	refluxing	VIIId-5	5.0
C ₆ H ₅ -Li	VII-0	1	refluxing	VIIId-1	3.1

hydrogens at range 0.7 to 2.5 (τ) in its NMR spectrum.

4-Cinnolinecarbonitrile (VII-0)

When a mixture of VII-0 and phenylmagnesium bromide was refluxed in benzene, the expected products such as **a**, **b**, and **c** type of the compounds were not isolated, and only the formation of 1-phenyl-4(1*H*)-cinnolinone (VIIId-1) was found, although the yield was very small. Similarly, the reaction of VII-0 with methylmagnesium iodide resulted only in the formation of 1-methyl-4(1*H*)-cinnolinone (VIIId-5) in small yield. Moreover, VII-0 was also reacted with phenyllithium to give VIIId-1. Each of VIIId-1 and VIIId-5 was, respectively, identified with authentic specimen^{24,25}) prepared by each specific route.

Discussion

In the reactions of V-0 and VI-0, **a**, **b**, and **c** type of the compounds were the expected products, and the formation of the **a**, **b**, and **c** type of the compounds are explained as follows; the addition of Grignard reagent to the ring carbon-nitrogen double bond, in which the carbon atom

Chart 5

24) H.J. Barber and E. Lunt, *J. Chem. Soc.*, 1964, 1468.

25) D.E. Ames and H.Z. Kucharska, *J. Chem. Soc.*, 1963, 4924.

is bound to cyano group, gives **a** type of the compound, the addition of Grignard reagent to cyano group forms acyl group (**b** type of the compound), and the addition of Grignard reagent to the ring carbon–nitrogen double bond, in which the carbon atom is not bound to cyano group, gives **c** type of the compound. The oxidation of an intermediate (**1c**) of **c** type of the compound forms **c'** type of the compound. But it is not clear as yet what substance acts as an electron acceptor in this oxidation step. For example, the possible formation mechanisms of **a**, **b**, **c**, and **c'** type of the compounds in V-0 are written as Chart 5.

In the reactions of V-0, VI-0, and VII-0 the formation of **d** type of the compound is characteristic of the Grignard reaction of cyanobenzodiazines except IV-0 giving only **a** type of the compound.⁵⁾ The possible mechanism of the formation of **d** type of the compound, with VIIId as a sample, is written as Chart 6. The addition of Grignard reagent to the ring nitrogen–nitrogen bond between the 1- and 2-positions forms an adduct **1d**, and the oxidation of **1d** leads to an intermediate (**2d**). Finally, VIIId is formed from **2d** through **3d**; that is, the addition of water to the 4-position of **2d** gives **3d** which forms VIIId with the loss of hydrogen cyanide. But it is not clear as yet what substance acts as an electron acceptor in this oxidation step.

The compound **Ve** (**e** type of the compound), which was the product peculiar to the Grignard reaction of V-0, originates from **1c** as mentioned in reference to the mechanism of the formation of **c** type of the compound. Thus, **1c** acts as Grignard reagent and adds to the ring carbon–nitrogen double bond between the 1- and 2-positions of unchanged V-0 to form an intermediate (**2e**) which leads to **Ve**, as shown in Chart 7. The similar reaction was reported by Ôishi and his co-workers as regards the Grignard reaction of 1-(methylsulfonyl)phthalazine (XII) giving 1-alkyl-1,2-dihydro-4-(methylsulfonyl)-2-(1-phthalazinyl)phthalazine (XIII).¹⁵⁾

Although it seems that the compounds Vf-4, Vg-4, and Vh-5 are the products involving 1 mole of V-0 and 2 or 3 moles of Grignard reagent, and that VIIi is formed by the radical course, the possible mechanisms of their formations have not been figured out yet.

Experimental²⁶⁾

IR spectra were recorded on a Jasco Grating Infrared Spectrophotometer Model IRA-1. NMR spectra were measured at 60 Mc and 23° on a Hitachi High Resolution NMR Spectrometer Model R-24 using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMS single focusing mass spectrometer. Samples were vaporized in all glass inlet system for the compounds having melting point below 150° and direct inlet system for those above 150°. Exact mass measurements were made on a JEOL JMS-01SG-2 mass spectrometer combined with a JEC-6 spectrum computer. Samples were vaporized in direct inlet system.

Reaction of V-0 with C_6H_5-MgBr — C_6H_5-MgBr was prepared by the usual method from 608 mg of bromobenzene and 160 mg of Mg in 10 ml of ether. This solution was gradually added to a solution of 500 mg of V-0 in 30 ml of THF with shaking. The mixture was refluxed for 3 hr. After cooling, NH_4Cl-NH_3 aqueous solution (a solution of 20 g of NH_4Cl and 4 ml of 28% NH_3 in 70 ml of H_2O) was added to the reaction mixture. The THF layer was separated from the aqueous solution. The aqueous solution was extracted with benzene, and the benzene extract was combined with the THF layer. After drying over anhyd. Na_2SO_4 , solvent was evaporated to dryness. The residue was chromatographed on a column of silica gel. The fraction eluted with benzene gave Vc-1 which was purified by recrystallization from petr. ether-benzene. The first, second, third, and fourth fractions eluted with $CHCl_3$ gave, respectively, Vc'-1,¹²⁾ mp 180—182° as slightly yellow needles from petr. ether-benzene, Ve-1,¹⁵⁾ mp 195° as yellow needles from petr. ether-benzene, V-O,⁶⁾ and Vb-1,¹¹⁾ mp 118—120° as slightly yellow needles from petr. ether-benzene. The yields of these products were shown in Table I. Melting point, elemental analysis, and IR spectrum of Vc-1 were shown in Table II, and its NMR spectrum was in Table III.

Reaction of V-0 with $C_6H_5CH_2-MgCl$ —To a solution of 500 mg of V-0 in 30 ml of THF, a solution of $C_6H_5CH_2-MgCl$ prepared from 500 mg of benzyl chloride and 160 mg of Mg in 20 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of V-0 with C_6H_5-MgBr . The elution with benzene gave Vc-2 which was recrystallized from petr. ether-benzene. The first, second, third, and fourth fractions eluted with $CHCl_3$ afforded, respectively, Ve-2 which was recrystallized from petr. ether-benzene, Vc'-2 which was recrystallized from petr. ether-benzene, V-O,⁶⁾ and Va-2,⁹⁾ picrate mp 150—151°. The yields of these products were shown in Table I. Melting points, elemental analyses, and IR spectra of Vc-2, Vc'-2, and Ve-2 were shown in Table II, and their NMR spectra were in Table III.

Reaction of V-0 with $(CH_3)_2CH-MgBr$ —To a solution of 500 mg of V-0 in 30 ml of THF, a solution of $(CH_3)_2CH-MgBr$ prepared from 500 mg of isopropyl bromide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of V-0 with C_6H_5-MgBr . The first and second fractions eluted with benzene gave, respectively, Vd-3 as colourless oil and Vc-3 as yellow oil. The first and second fractions eluted with $CHCl_3$ afforded, respectively, Va-3 as brown oil (picrate mp 159—160°) and V-O.⁶⁾ The yields of those products were shown in Table I. Elemental analyses, Mass, and IR spectra of Va-3, Vc-3, and Vd-3 were shown in Table II, and their NMR spectra were in Table III.

Reaction of V-0 with C_2H_5-MgBr —To a solution of 500 mg of V-0 in 30 ml of THF, a solution of C_2H_5-MgBr prepared from 430 mg of ethyl bromide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of V-0 with C_6H_5-MgBr . The first and second fractions eluted with benzene gave, respectively, Vg-4 as yellow oil and Vc-4 as yellow oil. The first and second elutions with $CHCl_3$ -benzene (1:1) afforded, respectively, Vd-4 which was recrystallized from petr. ether and V-O.⁶⁾ The first and second fractions eluted with $CHCl_3$ gave, respectively, Va-4,¹⁰⁾ picrate mp 175° (decomp.), and Vf-4,¹⁶⁾ mp 62° as slightly yellow needles from petr. ether. The yields of those products were shown in Table I. Melting point, Mass including exact mass measurement, and IR spectra of Vc-4, Vd-4, and Vg-4 were shown in Table II, and their NMR spectra were in Table III.

Reaction of V-0 with CH_3-MgI —To a solution of 500 mg of V-0 in 30 ml of THF, a solution of CH_3-MgI prepared from 550 mg of methyl iodide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of V-0 with C_6H_5-MgBr . The first, second, third, and fourth fractions eluted with benzene gave, respectively, Vh-5 which was recrystallized from petr. ether, Vc-5 which was recrystallized from petr. ether, Vc'-5,¹³⁾ mp 150—151° as slightly brownish needles from petr. ether-benzene, and Vd-5,¹⁴⁾ mp 113° as colourless plates from petr.

26) All melting points were not corrected.

ether. The elution with CHCl_3 gave **Ve-5**,¹⁵⁾ mp 168° as yellow needles from petr. ether–benzene. The yields of those product were shown in Table I. Melting points, elemental analyses, and IR spectra of **Vc-5** and **Vh-5** were shown in Table II, and their NMR spectra were in Table III.

Oxidation of Vc with $\text{K}_3\text{Fe}(\text{CN})_6$ —A mixture of 0.001 mole of **Vc** in 20 ml of benzene, 280 mg of KOH dissolved in 5 ml of H_2O , and 1316 mg of $\text{K}_3\text{Fe}(\text{CN})_6$ in 10 ml of H_2O was vigorously shaken for 2 hr at room temperature. After dried over anhyd. Na_2SO_4 , the evaporation of benzene gave **Vc'**.

Thus, 233 mg of **Vc-1** gave **Vc'-1**, mp 180–182° as pale yellow needles from petr. ether–benzene, in 81.5% yield (188 mg). This compound was identified with the authentic specimen¹²⁾ prepared from another route.

From 247 mg of **Vc-2**, **Vc'-2** was given in 78.1% yield (191 mg), mp 186–187° as colourless plates from petr. ether–benzene. Elemental analysis and IR spectrum of **Vc'-2** were shown in Table II, and its NMR spectrum was in Table III.

From 199 mg of **Vc-3**, **Vc'-3** was obtained in 75.6% yield (149 mg), mp 145–146° as yellow prisms from petr. ether. Elemental analysis and IR spectrum of **Vc'-3** were shown in Table II, and its NMR spectrum was in Table III.

From 185 mg of **Vc-4**, **Vc'-4** was formed in 50.8% yield (93 mg), mp 130° as colourless needles from petr. ether. Elemental analysis and IR spectrum of **Vc'-4** were shown in Table II, and its NMR spectrum was in Table III.

From 171 mg of **Vc-5**, **Vc'-5** was obtained in 51.5% yield (87 mg), mp 150–151° as pale brownish needles from petr. ether. This compound was identified with an authentic specimen¹³⁾ prepared from another route.

Preparation of Vd-3 and Vd-4—i) A mixture of 200 mg of **VIII**, 200 mg of K_2CO_3 , and 340 mg of isopropyl bromide in 10 ml of acetone was heated at 150° for 5 hr in a sealed tube. After cooling, acetone was removed and 20 ml of H_2O was added to the residue, which was extracted with benzene. The extract was dried over anhyd. Na_2SO_4 , and passed through a column of silica gel to give **Vd-3**, as oil, in 19.0% yield (49 mg). Mass and IR spectra of this compound were shown in Table II, and its NMR spectrum was in Table III.

ii) Similar reaction, using a mixture of 200 mg of **VIII**, 200 mg of K_2CO_3 , and 430 mg of ethyl bromide in 10 ml of acetone, gave **Vd-4**, mp 56° as colourless needles from petr. ether, in 22.0% yield (52 mg). Mass and IR spectra of this compound were shown in Table II, and its NMR spectrum was in Table III.

Reaction of IX with $\text{C}_6\text{H}_5\text{-MgBr}$ — $\text{C}_6\text{H}_5\text{-MgBr}$ was prepared by the usual method from 4000 mg of ethyl bromide and 1500 mg of Mg in 60 ml of ether. This solution was gradually added to a solution of 1800 mg of **IX** in 100 ml of benzene. The reaction mixture was refluxed for 2 hr. After cooling, $\text{NH}_4\text{Cl-NH}_3$ aqueous solution (120 g of NH_4Cl and 24 ml of 28% NH_3 in 400 ml of H_2O) was added to the reaction mixture. The benzene layer was dried over anhyd. Na_2SO_4 , and was chromatographed on a column of silica gel. The fraction eluted with benzene gave **X**, as oil, in 16.0% yield (321 mg). Mass and IR spectra of **X** were shown in Table II, and its NMR spectrum was in Table III. The fraction eluted with CHCl_3 gave **Vf-4**, mp 62° as slightly yellow needles from petr. ether, in 15.1% yield (253 mg). Picrate of this compound, mp 179° was identified with an authentic specimen¹⁶⁾ prepared from another route.

Reaction of VI-0 with $\text{C}_6\text{H}_5\text{-MgBr}$ — $\text{C}_6\text{H}_5\text{-MgBr}$ was prepared by the usual method from 608 mg of bromobenzene and 160 mg of Mg in 10 ml of ether. This solution was added in small portions to a solution of 500 mg of **VI-0** in 30 ml of THF with shaking. The mixture was refluxed for 3 hr. After cooling, $\text{NH}_4\text{Cl-NH}_3$ aqueous solution (20 g of NH_4Cl and 4 ml of 28% NH_3 in 70 ml of H_2O) was added. The THF layer was separated and aqueous solution was extracted with benzene. The extract was combined with the THF layer, and dried over anhyd. Na_2SO_4 . The residue, resulted from the evaporation of solvent, was chromatographed on a column of silica gel. The first, second, and third fractions eluted with benzene gave, respectively, **Vic'-1**,²¹⁾ mp 163° as colourless needles from petr. ether–benzene, **VI-0**,⁷⁾ and **Vib-1**,¹⁹⁾ mp 76–78° as slightly yellow needles from petr. ether. The fraction eluted with CHCl_3 afforded **Vi**. The yields of these products were in Table IV. Melting point and exact mass measurement of **Vii** were shown in Table V, and NMR spectrum of **Vii** were in Table VI.

Reaction of VI-0 with $\text{C}_6\text{H}_5\text{CH}_2\text{-MgCl}$ —To a solution of 500 mg of **VI-0** in 30 ml of THF, a solution of $\text{C}_6\text{H}_5\text{CH}_2\text{-MgCl}$ prepared from 500 mg of benzyl chloride and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of **VI-0** with $\text{C}_6\text{H}_5\text{-MgBr}$. The elution with benzene gave **Vic-2** which was recrystallized from benzene. The first and second fractions eluted with CHCl_3 gave, respectively, **Via-2**,¹⁷⁾ picrate mp 117°, and **Vid-2** which was recrystallized from petr. ether. The yields of these products were shown in Table IV. Melting points, elemental analyses, and IR spectra of **Vic-2** and **Vid-2** were shown in Table V, and their NMR spectra were in Table VI.

Reaction of VI-0 with $(\text{CH}_3)_2\text{CH-MgBr}$ —To a solution of 500 mg of **VI-0** in 30 ml of THF, a solution of $(\text{CH}_3)_2\text{CH-MgBr}$ prepared from 500 mg of isopropyl bromide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of **VI-0** with $\text{C}_6\text{H}_5\text{-MgBr}$. The first, second, and third fractions eluted with benzene gave, respectively, **Vic'-3** which was recrystallized from petr. ether, **Vic-3** which was recrystallized from petr. ether, and **VI-0**.⁷⁾ The elution with CHCl_3 gave **Vid-3** as oil. The yields of these products were shown in Table IV. Melting points, elemental analyses, Mass, and IR spectra of **Vic-3**, **Vic'-3**, and **Vid-3** were shown in Table V, and their NMR spectra were in Table VI.

Reaction of VI-0 with C_2H_5-MgBr —To a solution of 500 mg of VI-0 in 30 ml of THF, a solution of C_2H_5-MgBr prepared from 430 mg of ethyl bromide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of VI-0 with C_6H_5-MgBr . The first, second, and third fractions eluted with benzene gave, respectively, VIc-4,²²⁾ mp 93–94° as colourless needles from petr. ether, VI-c-4 which was recrystallized from petr. ether, and VI-0.⁷⁾ The first and second fractions eluted with $CHCl_3$ afforded, respectively, VIa-4,¹⁸⁾ picrate mp 123°, and VIId-4 which was recrystallized from petr. ether. The yields of these products were shown in Table IV. Melting points, elemental analyses, and IR spectra of VIc-4 and VIId-4 were shown in Table V, and their NMR spectra were in Table VI.

Reaction of VI-0 with CH_3-MgI —To a solution of 500 mg of VI-0 in 30 ml of THF, a solution of CH_3-MgI prepared from 550 mg of methyl iodide and 160 mg of Mg in 10 ml of ether was added, and the mixture was refluxed for 3 hr. The isolation procedure was carried out in the same fashion as for the reaction of VI-0 with C_6H_5-MgBr . The elution with benzene recovered VI-0.⁷⁾ The first and second fractions eluted with $CHCl_3$ gave, respectively, VIb-5,²⁰⁾ mp 77° as colourless needles from petr. ether, and VIId-5,²³⁾ mp 118–119° as slightly brownish needles from petr. ether. The yields of these products were shown in Table IV.

Preparation of VIId-4—A mixture of 200 mg of XI, 200 mg of K_2CO_3 , and 430 mg of ethyl bromide in 10 ml of acetone was heated at 150° for 5 hr in a sealed tube. After cooling, solvent was removed and 20 ml of H_2O was added to the residue. The mixture was then extracted with benzene. After dried over anhyd. Na_2SO_4 , the extract was passed through a column of silica gel to give VIId-4, mp 64–65° as colourless needles from petr. ether, in 13.0% yield (31 mg). Elemental analysis and IR spectrum of this compound were shown in Table V, and its NMR spectrum was in Table VI.

Reaction of VII-0 with C_6H_5-MgBr — C_6H_5-MgBr was prepared by the usual method from 1300 mg of bromobenzene and 400 mg of Mg in 7 ml of ether. This solution was gradually added to a solution of 500 mg of VII-0 in 15 ml of benzene, and the mixture was refluxed for 3 hr. After cooling, NH_4Cl-NH_3 aqueous solution (a solution of 5 g of NH_4Cl and 2 ml of 28% NH_3 in 20 ml of H_2O) was added, and the mixture was extracted with benzene. After dried over anhyd. Na_2SO_4 , the extract was passed through a column of alumina to give VIIId-1, mp 133–134° as orange yellow needles from isopropyl ether. The yield was shown in Table VII. This compound was identified with an authentic specimen²⁴⁾ prepared from another route.

Reaction of VII-0 with CH_3-MgI —To a solution of 500 mg of VII-0 in 15 ml of benzene, a solution of CH_3-MgI prepared from 700 mg of methyl iodide and 300 mg of Mg in 7 ml of ether was gradually added, and the mixture was refluxed for 1 hr. When the isolation procedure was carried out in the same fashion as for the reaction of VII-0 with C_6H_5-MgBr , VIIId-5 was given, mp 114–115° as colourless needles from isopropyl ether. The yield was shown in Table VII. This compound was identified with an authentic specimen²⁵⁾ prepared from another route.

Reaction of VII-0 with C_6H_5-Li —To a solution of 500 mg of VII-0 in 15 ml of benzene, a solution of C_6H_5-Li prepared from 1000 mg of bromobenzene and 150 mg of Li in 8 ml of ether was added, and the mixture was refluxed for 1 hr. When the isolation procedure was carried out in the same fashion as for the reaction of VII-0 with C_6H_5-MgBr , VIIId-1²⁴⁾ was obtained. The yield was shown in Table VII.

Acknowledgement We are greatly indebted both to the Ministry of Education, Science and Culture for the Grant-in-Aid of Scientific Research in 1975 and to the Ministry of Welfare for the Grant-in-Aid of Cancer Research in 1975.

Our thanks also goes to Mr. M. Uchida for Mass spectra, and to Miss H. Kawamura for microanalyses, in this college.