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The Reaction of Pyridazine 1-Oxide with Grignard Reagent

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A reaction of pyridazine 1-oxide with Grignard reagents prepared from bromobenzene, *p*-bromotoluene, *o*-bromotoluene, *m*-bromotoluene, *p*-bromoanisol and *o*-bromoanisol, gave the corresponding 1-aryl-*trans*-1-butene-3-yne (III) in about 30% yields. These structures were determined by in frared and nuclear magnetic resonance spectroscopy.

In 1940, a reaction of aromatic amine oxides with Grignard reagent was reported for the first time by Colonna[2] using pyridine or quinoline 1-oxide. It was re-examined by Ochiai and Arima,[3] and since then many reports have been published.[4] Main reaction is nucleophilic substitution reaction by Grignard reagents accompanying with deoxygenation from N-oxide group.[2,3,5] Diazine N-oxides, such as quinoxaline,[6] quinazoline[7] or phthalazine N-oxides[8] are substituted by alkyl- or aryl- group at α-position, without any deoxygenation, and when the α-position is occupied, the group enters into γ-position to the N-oxide. Further, Kato and Yamanaka[9] showed that a reaction of pyridine- or quinoline-1-oxide with phenylmagnesium bromide using tetrahydrofuran (THF) as the solvent gave the corresponding 1-hydroxy-2-phenyl-1,2-dihydro-pyridine or -quinoline as the main product, together with 2-phenylquinoline 1-oxide in the latter case. From these instances the reaction mechanism of aromatic amine oxides with Grignard reagent may be written in Chart 1 using quinoline 1-oxide as the example.

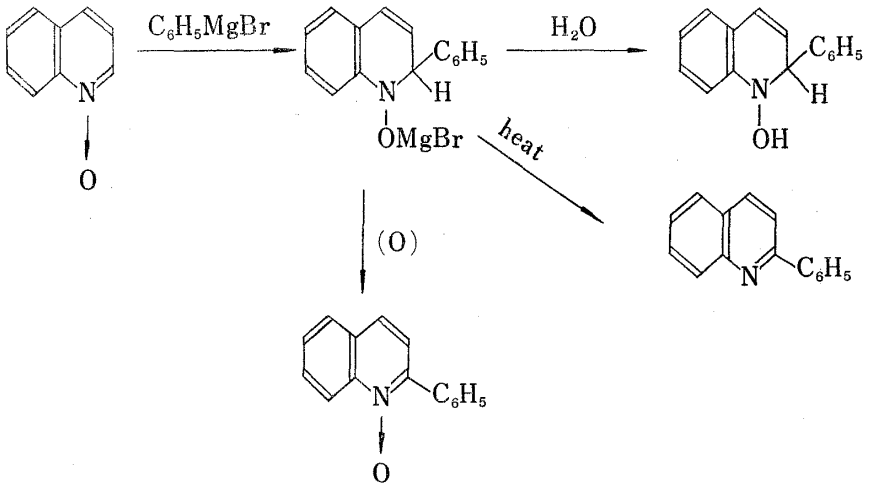


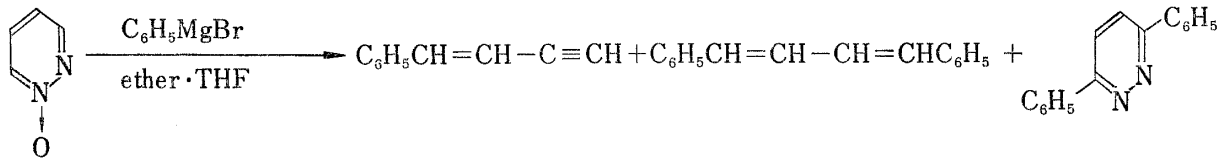
Chart 1

1) Location: *Turumaki, Setagaya, Tokyo.*
2) M. Colonna, *Boll. Sci. Fac. Chim. Ind. Bologna*, **4**, 134 (1940) [*C.A.*, **34**, 7290 (1940)].
3) E. Ochiai and K. Arima, *Yakugaku Zasshi*, **69**, 51 (1949).
4) E. Ochiai, "Aromatic Amine Oxides," Elsevir Publishing Co., Amsterdam, 1967, p. 251.
5) G. Kobayashi, *Yakugaku Zasshi*, **70**, 381 (1950).
6) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962).
7) E. Hayashi and T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **12**, 43 (1964).
8) E. Hayashi, E. Oishi, T. Tezuka and K. Ema, *Yakugaku Zasshi*, **88**, 1333 (1968).
9) T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965).

No Grignard reaction of pyridazine- or cinnoline N-oxide has been known. However, the reaction of pyridazine was reported by Letsinger and Lasco[10] to produce 4-substituted pyridazine. In the reaction of 3,6-disubstituted pyridazine, 3,6-disubstituted 4-alkyl-4,5-dihydropyridazine was the main product.[11] These products suggested that the reactions proceeded through 1,4-addition, which was different from the reactions of pyridine[12] and quinoline.[13]

Under these circumstances, it seemed interesting to examine whether the substituent enters into the α- or the γ-position to the N-oxide in pyridazine N-oxide. Some unexpected results in the experiments will be reported in this paper.

Firstly, phenylmagnesium bromide (IIa) was prepared in ether, and reacted with pyridazine 1-oxide (I) which had been dissolved in THF, at 15—20°. The mixture was treated as usual, and extracted with ether. The ether extracts were separated by chromatography through silica gel column, and 1,4-diphenyl-1,3-butadiene (IV) was obtained as the main product in about 28% yield, and 1-phenyl-1-butene-3-yne (IIIa) and 3,6-diphenylpyridazine (V) as the by–products in very small quantities.

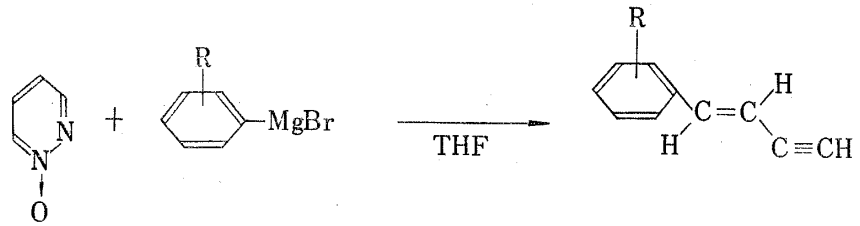


I IIIa IV V

Chart 2

Such compounds as IV and IIIa have not yet been produced in Grignard reaction of aromatic amine oxides, then, it seems likely the reaction mechanism is different from the usual Grignard reaction of aromatic amine oxides. Subsequently, in order to obtain phenylsubstituted product in a better yield, the reaction was performed with THF, which is said to give good results in Grignard reaction.[14]

Pyridazine 1-oxide (I) was reacted with a Grignard reagent (II) in THF at 0—5° and later left at room temperature. After hydrolyzed with ice water, the reaction mixture was



I II III

a : R=H, b : R=*p*-CH_3
c : R=*o*-CH_3, d : R=*m*-CH_3
e : R=*p*-OCH_3, f : R=*o*-OCH_3

Chart 3

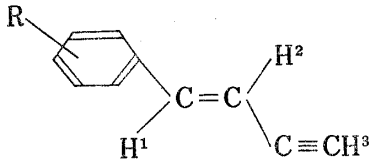
10) T.L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 812 (1956).
11) *a*) I. Crossland, *Acta Chem. Scand.*, **16**, 1877 (1956); *b*) A. Christensen and I. Crossland, *ibid.*, **17**, 1276 (1963); *c*) I. Crossland, *ibid.*, **18**, 1653 (1964); *d*) I. Crossland and L.K. Rasmussen, *ibid.*, **19**, 1652 (1965); *e*) L. Avellen, I. Crossland and K. Lund, *ibid.*, **21**, 2104 (1967); *f*) I. Crossland and E. Kelstrup, *ibid.*, **22**, 1669 (1968); *g*) I. Crossland and, *ibid.*, **22**, 2700 (1968).
12) R. Benkeser and D. Holton, *J. Am. Chem. Soc.*, **73**, 5861 (1951).
13) H. Gilman, J. Eisch and T. Soddy, *J. Am. Chem. Soc.*, **79**, 1245 (1957).
14) H. Normant, "Advances in Organic Chemistry," Vol. **2**, ed. by R.A. Raphael, E.C. Taylor and H. Wynberg, Intersciences Publishers, Inc., New York, N. Y., 1963, p. 1.

Table I. Basic Properties of 1-Aryl-*trans*-1-butene-3-ynes (IIIa—IIIf)

Comp. No.	R	bp (°C)	n_D^{20}	IR (liq. -cap.) cm^{-1} $\nu_{\equiv CH}$	$\nu_{C\equiv C}$	$\delta_{=CH}$
IIIa[a]	H	49—50 (2 mmHg)	1.6105	3300	2100	957
IIIb	*p*-CH_3	85—90 (6 mmHg)	1.5950	3300	2100	959
IIIc[b]	*o*-CH_3	47—49 (1 mmHg) (mp 40—42)	—	3280	2080	955
IIId	*m*-CH_3	73—74 (2 mmHg)	1.6033	3310	2100	959
IIIe[b]	*p*-OCH_3	66—69 (1 mmHg) (mp 47—49)	—	3300	2100	968
IIIf	*o*-OCH_3	71—72 (2 mmHg)	1.6098	3310	2100	959

a) lit.[15]; bp 55—75° (0.01 mmHg), n_D^{20} 1.6153 b) IR spectrum in KBr

Table II. The NMR Parameters (τ) for IIIa—IIIf in CCl_4



Comp. No.	H^1	H^2	H^3	R (CH_3 or OCH_3)
IIIa	3.13 d. (J=15.6 cps)	4.08 q. (J=15.6; 2.3 cps)	7.14 d. (J=2.3 cps)	—
IIIb	3.03 d. (J=15.6 cps)	4.05 q. (J=15.6; 2.3 cps)	7.15 d. (J=2.3 cps)	7.68 s.
IIIc	2.73 d. (J=15.6 cps)	4.03 q. (J=15.6; 2.3 cps)	7.12 d. (J=2.3 cps)	7.63 s.
IIId	3.10 d. (J=15.6 cps)	4.03 q. (J=15.6; 2.3 cps)	7.13 d. (J=2.3 cps)	7.70 s.
IIIe	3.09 d. (J=15.6 cps)	4.13 q. (J=15.6; 2.3 cps)	7.18 d. (J=2.3 cps)	6.23 s.
IIIf	3.03 d. (J=15.6 cps)	3.93 q. (J=15.6; 2.3 cps)	7.13 d. (J=2.3 cps)	6.17 s.

extracted with ether, and the extracts were purified by chromatography through silica gel column, the products were obtained in about 80% yields. The Grignard reagents (II) used were phenyl- (IIa), *p*-tolyl- (IIb), *o*-tolyl- (IIc), *m*-tolyl- (IId), *p*-methoxyphenyl- (IIe), and *o*-methoxyphenyl- (IIf) magnesium bromides. The products (III) were colored oils by vacuum distillation, which are described in Table I, II, and III with their physical data and the yields (8—35%).

The products (III) were found to be nitrogen-free by elemental analysis. The studies of the infrared (IR) spectra revealed that the band at about 3300 cm^{-1} was attributable to an acetylenic methin stretching vibration ($\nu_{\equiv CH}$), a band appearing at about 2100 cm^{-1} to $\nu_{C\equiv C}$, and a band at about 960 cm^{-1} to *trans* ethylenic bond $\delta_{C=H}$.

The nuclear magnetic resonance (NMR) spectrum of the product (IIIa) in carbon tetrachloride solution, as shown in Fig. 1, exhibited signals at 2.83 τ (5H, singlet, phenyl), at 3.13 τ (1H, doublet, J=15.6 cps, H^1), at 4.08 τ (1H, quartet, J=15.6 cps and 2.3 cps, H^2) and at 7.14 τ (1H, doublet, J=2.3 cps, H^3). The coupling constant $J_{2,1}$=15.6 cps is consistent with the coupling of two protons located in *trans* double bond. Furthermore, the coupling constant $J_{3,2}$=2.3 cps implies H^3 is a proton at the end of acetylenic bond.[15]

15) L.M. Jackmann, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85.

From these results, IIIa is considered to be 1-phenyl-*trans*-1-butene-3-yne, and the other physical data are not inconsistent with the figures in literatures.[16]

All the products IIIb—IIIf other than IIIa are also new compounds, NMR spectral data are shown in Table II.

On examining the ether extracts by thin-layer chromatography (TLC), a few spots of IV and V were found on the chromatograms, however, further examination was impossible because of the shortage of the samples. The only exception was in the case of IIf, from which anisol was obtained as the by-product in 4.2% yield.

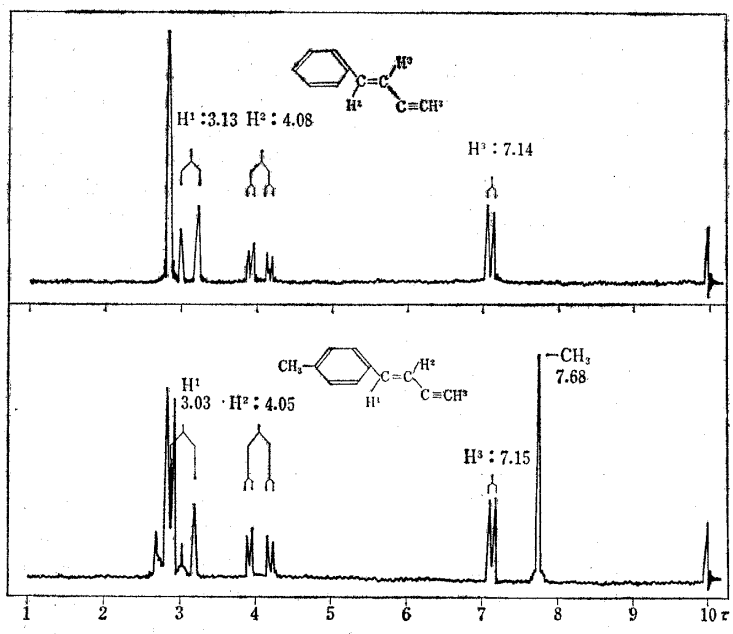


Fig. 1. The NMR Spectra of IIIa and IIIb in CCl_4

As the reaction mechanism, it may be said that addition of the aryl group at the α-position to N-oxide group at the first step, and the reaction further goes on. However, the later step is at present quite unknown. Now, the studies are in progress, which will be reported in the future.

Experimental[17]

Reaction of Pyridazine 1-Oxide (I) with Phenylmagnesium Bromide (IIa) in a Mixture of Ether and Tetrahydrofuran——To a stirred solution of phenylmagnesium bromide, prepared from 2.4 g (0.1 gram atom) of magnesium, 15.7 g (0.1 mole) of bromobenzene and 60 ml of dry ether, 5.8 g (0.06 mole) of pyridazine 1-oxide (I) dissolved in 30 ml of THF was added dropwise during about 30 min at 15—20°. The reaction mixture was allowed to stand overnight at room temperature, and treated with 100 ml of 20% ammonium chloride aqueous solution. The solution was extracted with ether several times, the combined ether extract was dried over anhyd. sodium sulfate. The ether was evaporated to dryness on a water bath, the tarry residue obtained was dissolved in benzene. The benzene solution was poured into a silica gel column, and the products were eluted with benzene.

From the first fraction, 4.5 g of red brownish residue was obtained. Recrystallization from ethanol gave 3.5 g (28%) of IV as colorless scales, mp 148—150°. This product was identical with the authentic 1,4-diphenyl-1,3-butadiene[18] by usual criteria. The filtrate on the recrystallization was evaporated to give red-brown oil. The presence of IIIa in this oily substance was proved by TLC, but further examination was impossible because of shortage of the sample.

From the second fraction eluted with benzene, 0.13 g of the colorless solid was obtained, and recrystallization from ethanol gave colorless scales, mp 229—231°. This product was identical with the authentic 3,6-diphenylpyridazine[19] by the usual criteria. Yield, 0.08 g (1%).

Reaction of Pyridazine 1-Oxide (I) with Arylmagnesium Bromides (IIa—IIf) in Tetrahydrofuran——To a stirred solution of IIa, prepared from 2.4 g (0.1 gram atom) of magnesium 15.7 g (0.1 mole) of bromobenzene in 30 ml of THF (prepared according to Kato and Yamanaka[9]), 5.8 g (0.06 mole) of I in 30 ml of THF was

16) Farbenfabriken Bayer A.G., Ger. Patent 1186063 (1965) [*C.A.* **62**, 14498 (1966)].
17) All melting points are uncorrected. IR spectra were measured on a Hitachi Model EPI S-2 spectrophotometer. NMR spectra were measured on a Japan Electron Optics Modes C-6OH spectrophotometer using tetramethylsilane as the internal standard.
18) B.B. Corson, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 229.
19) G.R. Ramage and J.K. Landquist, "Chemistry of Carbon Compounds," Vol. IV-B, ed. by E.H. Rodd, Elsevier Publishing Co., Amsterdam, 1959, pp. 1202—1205.

added dropwise for 30 min at 0—5°. The reaction mixture was left to stand for 30 min at the same temperature, and allowed to warm to room temperature (about 30 min). The mixture was decomposed by adding water, and neutralized with 10% hydrochloric acid solution. The aqueous solution was extracted with ether several times, the ether layers were dried over anhyd. sodium sulfate. The ether layers were evaporated and a red-brown tarry oil so obtained was dissolved in benzene and chromatographed through silica gel, and was eluted with benzene. By distilling the benzene off from the eluates, 6.3 g of the red-brown oil remained (81.4%). This crude substance was distilled to give 2.7 g (35.0%) of a strow-yellow oil, bp 49—50° (2 mmHg). Analytical data and physical data were shown in Table I, II and III.

Table III. Yield and Analytical Data of IIIa—IIIf

Comp. No.	Yield (%)		Formula	Analysis (%)			
				Calcd.		Found	
	Crude	Pure		C	H	C	H
IIIa	81.4	35.0	$C_{11}H_8$	93.71	6.29	93.62	6.25
IIIb	82.3	34.8	$C_{11}H_{10}$	92.91	7.09	92.73	7.06
IIIc	76.3	41.1	$C_{11}H_{10}$	92.91	7.09	92.74	7.05
IIId	62.3	30.7	$C_{11}H_{10}$	92.91	7.09	92.78	7.06
IIIe	15.7	8.4	$C_{11}H_{10}O$	83.51	6.37	83.44	6.35
IIIf[a)]		22.1	$C_{11}H_{10}O$	83.51	6.37	83.26	6.32

a) anisol: yield 4.2%.

The other compounds (IIIb—IIIf), listed in Table I, II and III, were prepared by treating in the same way as above mentioned.

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