[Chem. Pharm. Bull. 26(8)2550—2554(1978)]

UDC 547.852.2.04 : 547.559.4.04

Cross-Coupling Reaction of Chloropyridazines and Grignard Reagents with Nickel-phosphine Complexes: Alkylation and Arylation of Pyridazines

Akio Ohsawa, Yoshihito Abe, and Hiroshi Igeta

School of Pharmaceutical Sciences, Showa University[1]

(Received March 7, 1978)

Alkyl- and arylpyridazines have been prepared by cross-coupling reaction between chloropyridazines and Grignard reagents in the presence of nickel-phosphine complexes (as catalysts). Hitherto unaccessible naphthyl- and thienylpyridazines have been obtained.

Keywords——alkylpyridazines; arylpyridazines; thienylpyridazines; cross-coupling reaction; Grignard reagents; chloropyridazines; nickel-phosphine complex catalysis

The methods of the direct introduction of alkyl or aryl group, which have been applied to other heterocyclic systems; *i.e.*, pyridine and quinoline *etc.* suffer restriction in the case of pyridazines. Thus, Letsinger *et al.*[2] investigated phenylation and butylation of pyridazine using Grignard reagents and organolithiums, but the yields of (3- and 4-) phenylpyridazines, were unsatisfactory (Chart 1).

Igeta *et al.*[3] showed that the reaction of pyridazine N-oxides with Grignard reagents afforded the products of ring degradation besides 3-phenylpyridazine of low yield (Chart 2).

Crossland *et al.*[4] investigated the reaction of Grignard reagents with halogenated pyridazines and clarified that the alkylation proceeded at the 4- and 5-positions providing adducts instead of the cross-coupling reaction products (Chart 3).

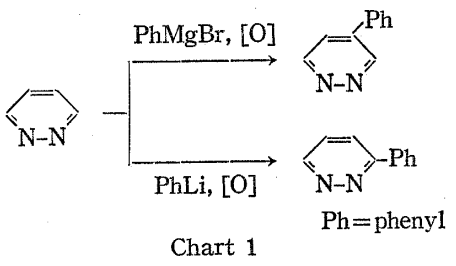

Chart 1

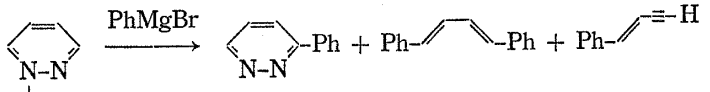

Chart 2

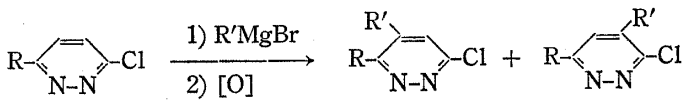

Chart 3

Meanwhile, the introduction of alkyl or aryl group into the pyridazine ring by the coupling reaction between halo-pyridazines and organometals is still a synthetically preferable method because many halo-pyridazines are the synthetic intermediates of some pyridazines and some of them are available with ease.

Recently, Tamao *et al.*[5] and Corriu *et al.*[6] found that aryl and vinyl halides reacted with Grignard reagents in the presence of nickel-phosphine complexes as catalysts to give cross-coupled products and the procedure has been applied to the alkylation and arylation of quinoline,[7] pyridine[8] and pyrimidine[9] series.

1) Location: *Hatanodai, Shinagawa-ku, Tokyo 142, Japan.*
2) R.L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 812 (1956).
3) H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Lett.*, **1969**, 2667.
4) L. Avellen and I. Crossland, *Acta Chem. Scand.*, **23**, 1887 (1969); I. Crossland and H. Kofod, *ibid.*, **24**, 751 (1970).

We have attempted to apply this reaction to the syntheses of alkyl- and arylpyridazines and obtained various pyridazines of the cross-coupled products, some of whose preparations are not easy by other known procedures.

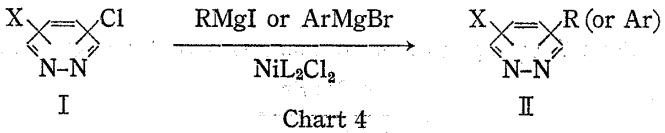

Chart 4

The reaction was carried out in ether in the presence of catalytic amount of dichloro-[1,2-bis(diphenylphosphine)propane]nickel, [Ni(dppp)Cl_2][5] for the alkylation, and dichloro-[1,2-bis(diphenylphosphine)ethane]nickel, [Ni(dppe)Cl_2][5] for arylation. In most cases the reaction was performed by heating the mixture to reflux while in some runs the reaction was exothermic and the heating was unnecessary.

The yields(isolated) of the cross-coupled products with methyl- and ethylmagnesium iodides are summarized in Table I.

Table I. Cross-Coupling of Chloropyridazines with Alkylmagnesium Iodides

$$\text{I} \xrightarrow[\text{Ni(dppp)Cl}_2]{\text{RMgI}} \text{II}$$

I	RMgI	II	Yields (%)
3-Cl-6-Me	MeMgI	3,6-diMe[a]	71
	EtMgI	3-Et-6-Me[b]	20
3-Cl-6-Ph	MeMgI	3-Me-6-Ph[c]	74
	EtMgI	3-Et-6-Ph	38
3-Cl-6-MeO	MeMgI	3-Me-6-MeO[d]	24
	EtMgI	3-Et-6-MeO	unisolable
3-Cl-6-$N(CH_2)_5$	MeMgI	3-Me-6-$N(CH_2)_5$[e]	quantitative
	EtMgI	3-Et-6-$N(CH_2)_5$	51
3-Cl-4-Me	MeMgI	3,4-diMe[f]	62
	EtMgI	3-Et-4-Me	33
4-Cl-3,6-diMe	MeMgI	3,4,6-triMe[g]	25
	EtMgI	3,6-diMe-4-Et	unisolable

a) C.G. Overberger, N.R. Byrd, and R.B. Mesrobian, *J. Am. Chem. Soc.*, **78**, 1961 (1956).
b) K.N. Zelenin and I.P. Bezhan, *Dokl. Akad. Nauk SSSR*, **191**, 1292 (1970) [*C.A.* **73**, 35307 *q* (1970)].
c) J. Levisalles and P. Baranger, *Compt. Rend.*, **238**, 592 (1954).
d) W.G. Overend, L.M. Turton, and L.F. Wiggins, *J. Chem. Soc.*, **1950**, 3500.
e) N.K. Basu and F.L. Rose, *J. Chem. Soc.*, **1963**, 5660.
f) J. Levisalles, *Bull. Soc. Chim. Fr.*, **1957**, 1009.
g) J. Levisalles and P. Baranger, *Compt. Rend.*, **242**, 1336 (1956).

Methylmagnesium iodide showed higher reactivity than ethylmagnesium iodide towards chloropyridazines under the mentioned conditions. Considerable yields were obtained in most cases whereas ethylation of 3-chloro-6-methoxy- and 4-chloro-3,6-dimethylpyridazines did not afford the expected products and the reason is not clear.[10]

Additionally, the reaction of methylmagnesium iodide with 3,6-dichloropyridazine in the presence of Ni(dppp)Cl_2 or Ni(dppe)Cl_2 afforded 3,6-dimethylpyridazine in low yield.

5) K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972); K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, **49**, 1958 (1976).
6) R.J.P. Corriu and J.P. Masse, *J. Chem. Soc., Chem. Commun.*, **1972**, 144.
7) E.D. Thorsett and F.R. Stermitz, *J. Heterocycl. Chem.*, **10**, 243 (1973).
8) L.N. Pridgen, *J. Heterocycl. Chem.*, **12**, 443 (1975).
9) H. Yamanaka, K. Edo, M. Konno, and M. Mizugaki, The 97th Annual Meeting of Pharm. Soc. of Japan, Apr. 1977.
10) In most cases, the recovery of the starting materials was negligible.

Next, the arylation with phenyl-, naphthyl (Np)-, and thienyl(Tp)magnesium bromides was examined [cat.: $Ni(dppe)Cl_2$].

The results are collected in Table II.

Table II. Cross-Coupling of Chloropyridazines with Arylmagnesium Bromides

$$\text{I} \xrightarrow[Ni(dppe)Cl_2]{ArMgBr} \text{II}$$

I	ArMgBr	II	Yields (%)
3-Cl-6-Me	PhMgBr	3-Me-6-Ph[a]	68
	α-NpMgBr	3-Me-6(2′-Np)	55[b]
	α-TpMgBr	3-Me-6(2′-Tp)	79
3-Cl-6-Ph	PhMgBr	3,6-diph[c]	50
	α-NpMgBr	3(2′-Np)-6-Ph	70
	α-TpMgBr	3-Ph-6-(2′-Tp)	78
3-Cl-6-MeO	PhMgBr	3-MeO-6-Ph[d]	5
	α-NpMgBr	3-MeO-6(2′-Np)	unisolable
	α-TpMgBr	3-MeO-6-(2′-Tp)	79
3-Cl-6-$N(CH_2)_5$	PhMgBr	3-$N(CH_2)_5$-6-Ph	60
	α-NpMgBr	3-$N(CH_2)_5$-6(2′-Np)	72
	α-TpMgBr	3-$N(CH_2)_5$-6(2′-Tp)	65
3-Cl-4-Me	PhMgBr	4-Me-3-Ph	8
	α-NpMgBr	4-Me-3(2′-Np)	unisolable
	α-TpMgBr	4-Me-3(2′-Tp)	66
4-Cl-3,6-diMe	PhMgBr	3,6-diMe-4-Ph	9
	α-NpMgBr	3,6-diMe-4(2′-Np)	7
	α-TpMgBr	3,6-diMe-4(2′-Tp)	27

a) Footnote c) in Table I.
b) Yield of crude material is shown, for this compound.
c) P. Baranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, **1957**, 704.
d) I. Crossland and L. K. Rasmussen, *Acta Chem. Scand.*, **19**, 1652 (1965).

Moderate yields were obtained in most cases with some exceptional runs in which the expected products were not obtained in satisfactory yields by ambiguous reason.[10] The efficiency of arylation was in the order: α-TpMgBr>PhMgBr>α-NpMgBr in general, where the presence of steric effect is suggested.

The reaction mentioned here did not proceed in absence of the catalyst and the recovery of the starting materials was observed. Thus, the cross-coupling reaction using nickel-phosphine complexes as catalysts is a potential and general method to prepare pyridazine derivatives because some alkyl- and arylpyridazines are difficult to synthesize by other procedures and chloropyridazines are easy to prepare.

We also could synthesize a new type of pyridazine derivatives possessing a thienyl group.

Experimental

The products were identified by means of the melting points of the mixture of the samples (or their picrates) and their authentic samples if available. Other unknown products were determined by the elemental analyses of the materials and by their nuclear magnetic resonance (NMR) spectra. Properties of some products are listed in Table III. All melting and boiling points are uncorrected. NMR spectra were recorded on Hitachi R-20 and R-22 instruments.

The reaction was carried out according to the procedure described by Thorsett *et al.*[7] with slight modifications.

1. General Procedure——A solution of a chloropyridazine dissolved in an appropriate amount of ether was added to the ethereal solution of the Grignard reagent (prepared from 2 molar equiv., towards the chloropyridazine, of Mg and 2 molar equiv. of the alkyl or aryl halide) containing 0.01 molar equiv. of Ni-phosphine complex. The mixture was heated to reflux unless the reaction was exothermic. The mixture

TABLE III. Properties of Alkyl- and Arylpyridazines

II	mp (°C)	bp (°C/mm)	Picrate mp (°C)	Analysis (%) Found (Calcd.) C	H	N	NMR (δ, J in Hz)
3,6-diMe	Oil	77/2 (52/1) [a]					2.64 (6H, s), 7.20 (2H, s)
3-Et-6-Me	Oil	105—110/4 (81.5/2.5) [b]	107.5—109.5				
3-Me-6-Ph	104—105 (103) [c]						
3-Et-6-Ph	68—69			77.97 (78.23	6.53 6.57	15.17 15.21)	1.32 (3H, t, 7.5), 2.96 (2H, q, 7.5), 7.28 (1H, d, 9.0), 7.3—7.6 (3H, m), 7.70 (1H, d, 9.0), 7.9—8.2 (2H, m)
3-Me-6-MeO	Oil	102—104/18 (210/760) [d]					
3-Me-6-N$(CH_2)_5$	61—62 (63—65) [e]			68.01 (67.76	8.70 8.53	23.39 23.71)	1.62 (6H, br. m), 2.50 (3H, s), 3.55 (4H, br.m) 6.80 (1H, d, 9.9), 7.06 (1H, d, 9.9)
3-Et-6-N$(CH_2)_5$	Oil	150/0.01	163—164	48.89 (Picrate) (48.57	4.80 4.80	19.84 19.99)	1.28 (3H, t, 7.5), 1.60 (6H, br.m), 2.80 (2H, q, 7.5), 3.56 (4H, br.m), 6.80 (1H, d, 10.2), 7.12 (1H, d, 10.2)
3,4-diMe	43—44 (44) [f]		174—175 (174) [f]				
3-Et-4-Me	*ca.* 30		100—101	44.67 (Picrate) (44.45	3.66 3.73	19.86 19.94)	1.32 (3H, t, 7.2), 2.32 (3H, s), 2.96 (2H, q, 7.2), 7.24 (1H, d, 5.1), 8.24 (1H, d, 5.1)
3,4,6-triMe	90—91 (93—94) [g]			68.81 (68.82	8.26 8.25	22.88 22.93)	2.22 (3H, s), 2.58 (6H, s), 7.06 (1H, s)
3-Me-6(2′-Np)	84—85		174	81.64 (81.79	5.54 5.49	12.72 12.72)	2.75 (3H, s), 7.2—8.1 (9H, m)
3-Me-6(2′-Tp)	157—158			61.27 (61.34	4.63 4.58	15.87 15.90)	2.66 (3H, s), 7.0—7.8 (5H, m)
3,6-diPh	216—217 (225) [h]						
3(2′-Np)-6-Ph	167—168			84.69 (85.08	5.06 5.00	10.03 9.92)	7.0—8.4 (m)
3-Ph-6(2′-Tp)	162			69.10 (69.39	4.21 4.16	11.35 11.56)	7.0—8.2 (m)
3-MeO-6-Ph	113—114 (116—118) [i]						
3-MeO-6(2′-Tp)	75—76			56.43 (56.23	4.36 4.19	14.51 14.57)	4.12 (3H, s), 6.8—7.8 (5H, m)
3-N$(CH_2)_5$-6-Ph	131—132			75.00 (75.28	7.23 7.16	17.28 17.56)	1.66 (6H, br. m), 3.64 (4H, br. m), 6.88 (1H, d, 9.3), 7.2—7.5 (3H, m), 7.56 (1H, d, 9.3), 7.8—8.1 (2H, m)
3-N$(CH_2)_5$-6(2′-Np)	115—116			79.06 (78.86	6.59 6.62	14.44 14.52)	1.66 (6H, br.m), 3.64 (4H, br.m), 6.88 (1H, d, 9.9), 7.2—8.3 (8H, m)
3-N$(CH_2)_5$-6(2′-Tp)	116			63.77 (63.64	6.16 6.16	17.17 17.17)	1.64 (6H, br. m), 3.60 (4H, br. m), 6.7—7.6 (5H, m)
4-Me-3-Ph	Oil			M^+ by MS; 170.0842 (170.0844)			2.36 (3H, s), 7.36 (1H, d, 6.0), 7.54 (5H, m), 9.02 (1H, d, 6.0)
4-Me-3(2′-Tp)	122—123			61.10 (61.34	4.61 4.58	16.00 15.90)	2.50 (3H, s), 7.0—7.7 (4H, m), 8.88 (1H, d, 4.8)
3,6-diMe-4-Ph	Oil	165—170/2	136—137	51.99 (Picrate) (52.30	3.58 3.66	17.02 16.94)	2.58 (3H, s), 2.64 (3H, s), 7.0—7.5 (6H, m)
3,6-diMe-4(2′-Np)	Oil		162	57.29 (Picrate) (57.02	3.70 3.70	14.65 15.11)	2.40 (3H, s), 2.74 (3H, s), 7.0—8.2 (8H, m)
3,6-diMe-4(2′-Tp)	Oil	150/2	186	46.09 (Picrate) (45.82	3.12 3.12	16.51 16.69)	2.64 (3H, s), 2.78 (3H, s), 7.0—7.6 (4H, m)

a)—*g*) Correspond to footnotes *a*)—*g*) in Table I, respectively.
h) Footnote *c*) in Table II.
i) Footnote *d*) in Table II.

was quenched by aq. HCl, neutralized by K_2CO_3 and submitted to the appropriate work-up. The typical procedures are shown next.

Reaction of 3-Chloro-6-methylpyridazine with Methylmagnesium Iodide: $Ni(dppp)Cl_2$ (108 mg) was added to an ethereal solution of MeMgI prepared from Mg (1.1 g) and MeI (6.2 g) in ether (20 ml). Then a solution of 3-chloro-6-methylpyridazine (2.6 g) in ether (60 ml) was added dropwise to the reaction mixture with stirring under nitrogen atmosphere. The mixture was refluxed for 3 hr and quenched by HCl–ice-water. After neutralization by aq. K_2CO_3 (till the mixture became slightly alkaline), the ethereal layer was separated and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined, dried over K_2CO_3 and evaporated to dryness. The residue was chromatographed on a short column of aluminum oxide (benzene) to give 1.51 g (71%) of essentially pure 3,6-dimethylpyridazine. Further purification was performed by distillation (bp 77°/2 mmHg).

Reaction of 3-Chloro-4-methylpyridazine with Methylmagnesium Iodide: $Ni(dppp)Cl_2$ (54 mg) was added to a solution of a Grignard reagent prepared from 0.55 g of Mg and 3.1 g of MeI in 20 ml of $(C_2H_5)_2O$. The reaction proceeded exothermally during the dropwise addition of a solution of 1.3 g of 3-chloro-4-methylpyridazine in 20 ml of $(C_2H_5)_2O$ to the mixture. And the mixture was stirred for 3 hr at room temperature. The mixture was worked up as described before, and the residue was submitted to a short column of aluminum oxide. 3,4-Dimethylpyridazine (0.68 g, 62%) was obtained as colourless needles of mp 43—44° after recrystallization (from CCl_4–hexane) of the eluted product. Picrate mp 174—175°.

2. **Reaction of 4-Chloro-3,6-dimethylpyridazine with Ethylmagnesium Iodide**——$Ni(dppp)Cl_2$ (27 mg) and 4-chloro-3,6-dimethylpyridazine (0.71 g) were handled in the same manner as in **1** with EtMgI from 0.28 g of Mg and 1.6 g of EtI in 20 ml of $(C_2H_5)_2O$. The mixture was refluxed for 3 hr and worked up as similar as described in **1**. The NMR spectrum of the resulting residue showed presence of neither remarkable product nor the starting material. No isolable product or the starting material was obtained despite a cautious separation of the mixture on aluminum oxide column. Other several runs with some modifications also did not give the expected product.

3. **Reaction of 3,6-Dichloropyridazine with Methylmagnesium Iodide**——$Ni(dppp)Cl_2$ (108 mg) and 3,6-dichloropyridazine (3.0 g) were treated with MeMgI (1.6 g of Mg and 9.4 g of MeI in 20 ml of$(C_2H_5)_2O$) as described in **1**. After being refluxed for 3 hr, the mixture was treated as same as in **1** and submitted to an aluminum oxide column chromatography. Three major fractions *i.e.*, 3,6-dichloro-4-methylpyridazine (50 mg), which was identified with the authentic sample,[11] 3,6-dimethylpyridazine (200 mg, 19%), and unidentified product (150 mg) of colourless needles (iso-Pr_2O–hexane) of mp 91.5—92.5° were obtained, whereas 3-chloro-6-methylpyridazine was not isolated.

Acknowledgement We wish to thank Prof. M. Ishikawa and Dr. Y. Komoda of Tokyo Medical and Dental Univ. for their arrangement for measurement of high resolution mass spectra of samples, and also to thank Prof. H. Yamanaka and Mr. K. Edo of Tohoku Univ. for providing Ni-phosphine complexes.

11) D.J. Durey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 37, 121 (1954).