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Studies on Pyrimidine Derivatives. VII.[1] Nickel-Phosphine Complex-Catalyzed Grignard Coupling of Chloropyrimidines

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In the presence of a nickel phosphine complex, the coupling reaction of Grignard reagents with chloropyrimidines such as 2-chloro-4,6-dimethyl- (III), 4-chloro-2,6-dimethyl- (V), 4,6-dichloro-2-methyl- (VIII), 2,4-dichloro-6-methyl- (X), and 2,4,6-trichloro-pyrimidine (XIII) was studied to give the corresponding alkyl (or arkyl) substituted pyrimidines in yields ranging from 40 to 88%. Although in the cases of VIII, X, and XIII, the selectivity on the reaction due to the position of the chloride atom was not observed, this coupling was concluded to remove the defects of the Pinner reaction for the synthesis of polyalkyl(or polyaryl)pyrimidines.

Keywords——Grignard coupling; nickel phosphine complex; polyalkylpyrimidine; 2-(β-ethoxyethyl))-6-methyl-4-pyrimidinone; 4-chloro-6-methyl-2-vinylpyrimidine

A number of studies on the utility of alkyl or aryl pyrimidines for synthesis of derivatives with a useful side chain have been delineated. For instance, 4-cyanopyrimidines, β-(2-pyrimidinyl)acrylic acid (I) and lathyrine (an α-amino acid with a 4-pyrimidinyl group) (II) were synthesized from simple pyrimidines.[3a–c]

While most alkyl or aryl pyrimidines can be prepared by condensation of β-diketones with amidines containing the required group already in place, this method is restricted in the following cases.[4]

(A) When amidines contain a long alkyl chain, the Pinner reaction with β-diketones shows a marked tendency of decreasing the yield.

(B) When benzoylketones are used as the β-diketone partner, the condensation with alkylamidines gives rise to the product in poor yield.

(C) β-Diketones leading to unsymmetrically substituted pyrimidines are not always easily accessible.

Recently, Kumada *et al.*[5] reported that the coupling reaction of 2-bromopyridine with Grignard reagents was strikingly promoted by the addition of nickel phosphine complexes, such as $Ni(Ph_2PCH_2CH_2PPh_2)Cl_2$, [abbreviated as $Ni(dppe)Cl_2$] and $Ni[(Ph_2PCH_2)_2CH_2]Cl_2$, [abbreviated as $Ni(dppp)Cl_2$]. This report stimulated us into studies on the coupling reaction of chloropyrimidines with alkylmagnesium or arylmagnesium halides,[6] because this reaction may remove the three difficulties in the pyrimidine formation described above. In this

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[1] Part VI: H. Yamanaka, H. Abe, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 842 (1978).

[2] Location: *Aobayama Sendai 980, Japan.*

[3] a) H. Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, *Chem. Pharm. Bull.* (Tokyo), **25**, 821 (1977); b) A. Jones, B. Kornfeld, and C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950); c) E.A. Bell and R.G. Foster, *J. Org. Chem.*, **30**, 115 (1965).

[4] D.J. Brown, "The pyrimidines," John Wiley and Sons. Inc., New York, 1962, pp. 116—137 and "The Pyrimidines Supplement I" pp. 86—93.

[5] K. Tamao, S. Kodama, T. Nakatsuka, Y. Kiso, and M. Kumada, *J. Am. Chem. Soc.*, **97**, 4405 (1975).

[6] Good yields in the Grignard coupling of chloropyrimidines were not observed when the reaction was performed without adding a catalyst. [H. R.Henze, W.J. Clegg, and C.W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).]

paper we wish to report the application of this method to the synthesis of polyalkyl (or polyaryl)pyrimidines from monochloro-, dichloro- and trichloropyrimidines.

According to the method reported by Kumada *et al.*,[5] 2-chloro-4,6-dimethylpyrimidine (III) was treated with alkyl(or aryl)magnesium halides in the presence of a catalytic amount of Ni(dppe)Cl_2 in boiling ether for 20 hr to give 2-alkyl(or aryl)-4,6-dimethylpyrimidines (IVa—e) in yields ranging from 48 to 74% (Table I).

Although III was not converted to 2-benzyl-4,6-dimethylpyrimidine (IVf) using these reaction conditions, IVf was obtained by use of larger quantities of Ni(dppp)Cl_2 and prolonged stirring of the reaction mixture at room temperature.

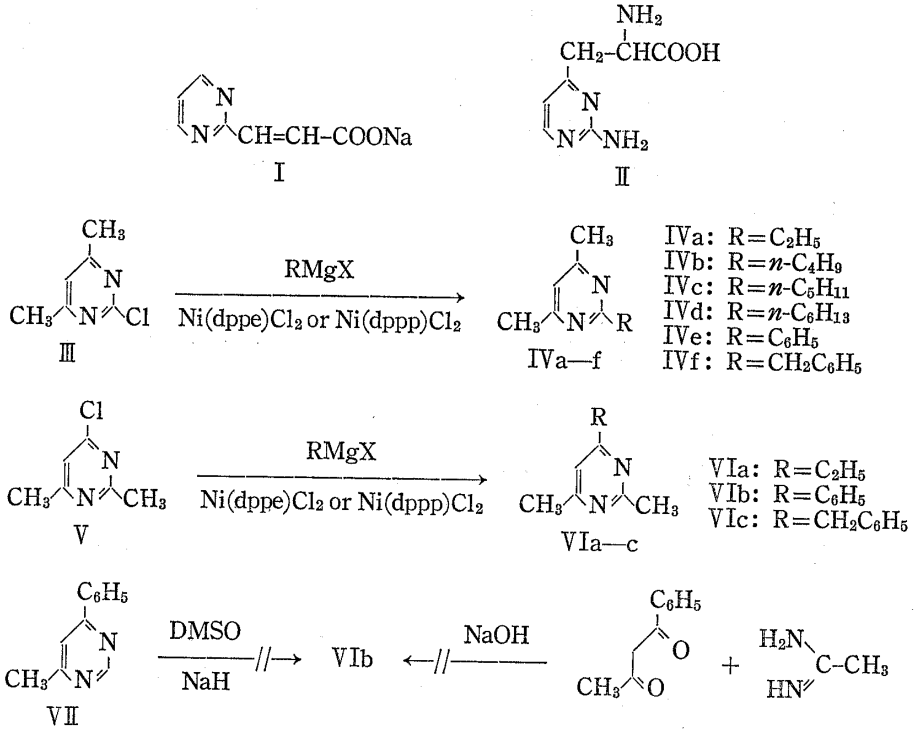

Chart 1

Table I. Melting Points, Boiling Points, and Yield of Compounds IVa—f, VIa—c, XIa, b, XIIa, b, XIVa, b

No.	mp (°C)	bp (°C)	Yield (%)	No.	mp (°C)	bp (°C)	Yield (%)
IVa		85 (27 mmHg)	74	VIc	48—49.5	130 (15 mmHg)	53
IVb		95 (16 mmHg)	67	XIa		132—135 (15 mmHg)	88
IVc		85 (4 mmHg)	64	XIb	96—97		66
IVd		85 (4 mmHg)	54	XIIa		125 (100 mmHg)	85
IVe	83—84[a]	163 (17 mHmg)	48	XIIb	93.5—95[d]	180—185 (2 mmHg)	63
IVf	80[b]	125 (4 mmHg)	46	XIVa		120 (80 mmHg)	40
VIa		85 (28 mmHg)[c]	61	XIVb	184[e]		56
VIb		124 (4 mmHg)	81				

a) Lit.[4] mp 83—84°.
b) Lit.[14] mp 80°.
c) Lit.[14] bp 72—76 (11 mmHg).
d) Lit.[15] mp 93—94°.
e) Lit.[16] mp 184°.

By comparison with the usual Pinner reaction,7) this Grignard coupling has a clear advantage in the synthesis of pyrimidines containing a long normal alkyl substituent at the 2-position.

In a similar fashion, 4-chloro-2,6-dimethylpyrimidine (V) was coupled with alkylmagnesium or arylmagnesium halide to afford 4-alkyl(or aryl)-2,6-dimethylpyrimidines (VIa—c). The yields of VIa—c obtained by this method are listed in Table I. Since the introduction of Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane) facilitates the synthesis of β-ketoesters,8) it is concluded that this coupling reaction provides the best way to prepare derivatives with different alkyl groups at the 4- and 6-positions.

Then in order to examine the scope and limitation of this reaction, the coupling of 4,6-dichloro-2-methyl- (VIII), 2,4-dichloro-6-methyl- (X), and 2,4,6-trichloropyrimidine (XIII) with a Grignard reagent was tested. When VIII was treated with one molar equivalent of methylmagnesium iodide, a mixture containing 2,4,6-trimethylpyrimidine (IX) and V was obtained along with starting material (VIII). Gas–liquid chromatographic analysis showed the ratio of IX: V: VIII in the mixture to be 2: 1: 5. The reaction of X with one molar equivalent of methylmagnesium iodide also afforded a mixture of IX, III, V, and X in a ratio of 3: 3: 1: 20.

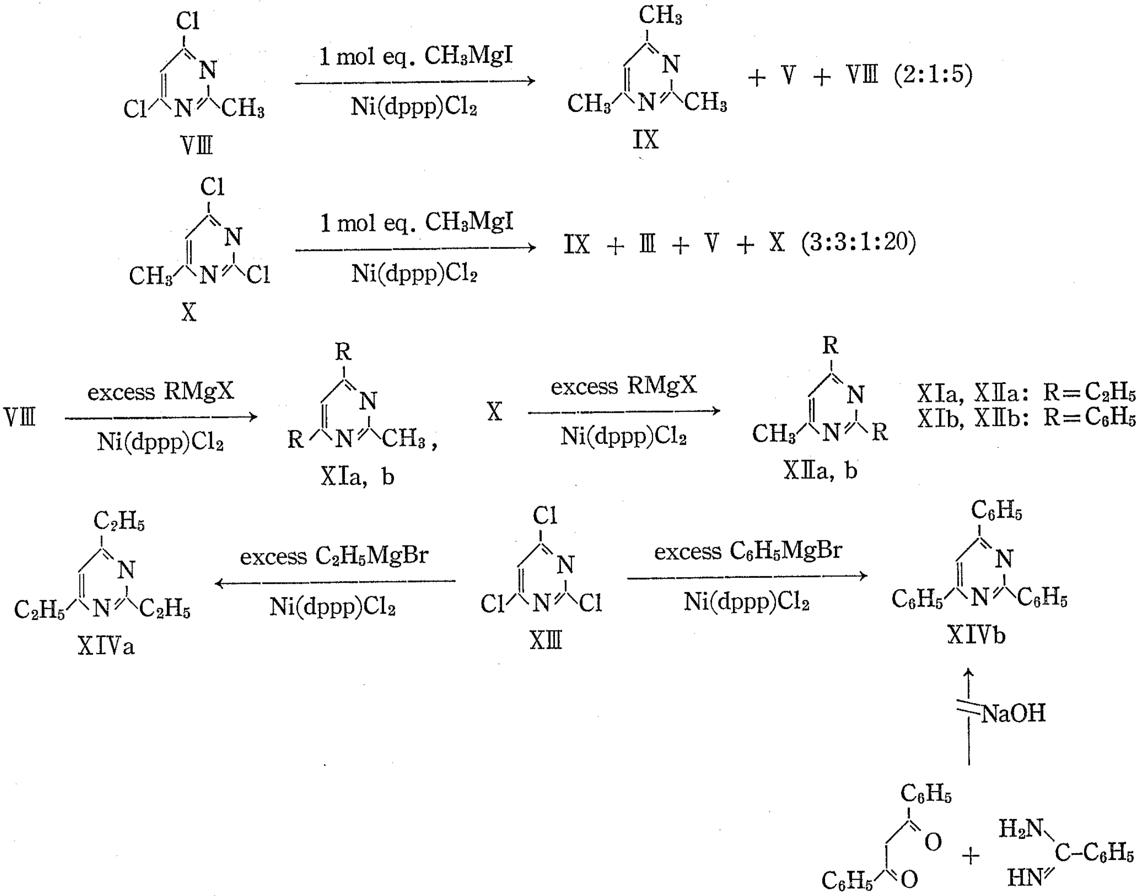

Chart 2

As shown in Chart 2, the reactions of excess Grignard reagents with di- or tri-chloropyrimidines (VIII, X, XIII) gave the corresponding trisubstituted pyrimidines (XIa, b, XIIa, b, XIVa, b) as sole products.

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7) A. Pinner, *Ber.*, **21**, 2122 (1893).

8) O. Yonemitsu and Y. Oikawa, private commmunication.

As most chloropyrimidines were easily accessible from the corresponding pyrimidinones in high yield, the transformation of the chloropyrimidines to alkyl(or aryl)pyrimidines in this manner is of wide application. For instance, condensation of benzoylacetone or benzalacetone with acetamidine, methylation of 4-methyl-6-phenylpyrimidine (VII) with dimethylsulfoxide-sodium hydride, or homolytic methylation of VII by various methods failed to give 2,6-dimethyl-4-phenylpyrimidine (VIb). However, the coupling of V with phenylmagnesium bromide in the presence of $Ni(dppp)Cl_2$ smoothly afforded VIb in 80% yield (Chart 1). The reaction of XIII with excess phenylmagnesium bromide gave a good yield of 2,4,6-triphenylpyrimidine (XIVb) which could not be obtained by the Pinner reaction (Chart 2).

Further, 2-(β-ethoxyethyl)-4,6-dimethylpyrimidine (XV) which was considered to be a precursor of 4,6-dimethyl-2-vinylpyrimidine, was easily prepared from 4-chloro-2-(β-ethoxyethyl)-6-methylpyrimidine (XVI) through this method. Namely, condensation of β-ethoxypropionamidine hydrochloride (XVII) with acetylacetone in a basic medium gave none of pyrimidine derivatives. On the contrary, ethyl acetoacetate reacted with XVII under the usual conditions to afford 2-(β-ethoxyethyl)-6-methyl-4-pyrimidinone (XVIII) in 67% yield. Chlorination of XVIII with phosphoryl chloride in boiling chloroform afforded XVI which coupled with methylmagnesium iodide in the presence of $Ni(dppp)Cl_2$ to give XV in 73% yield.

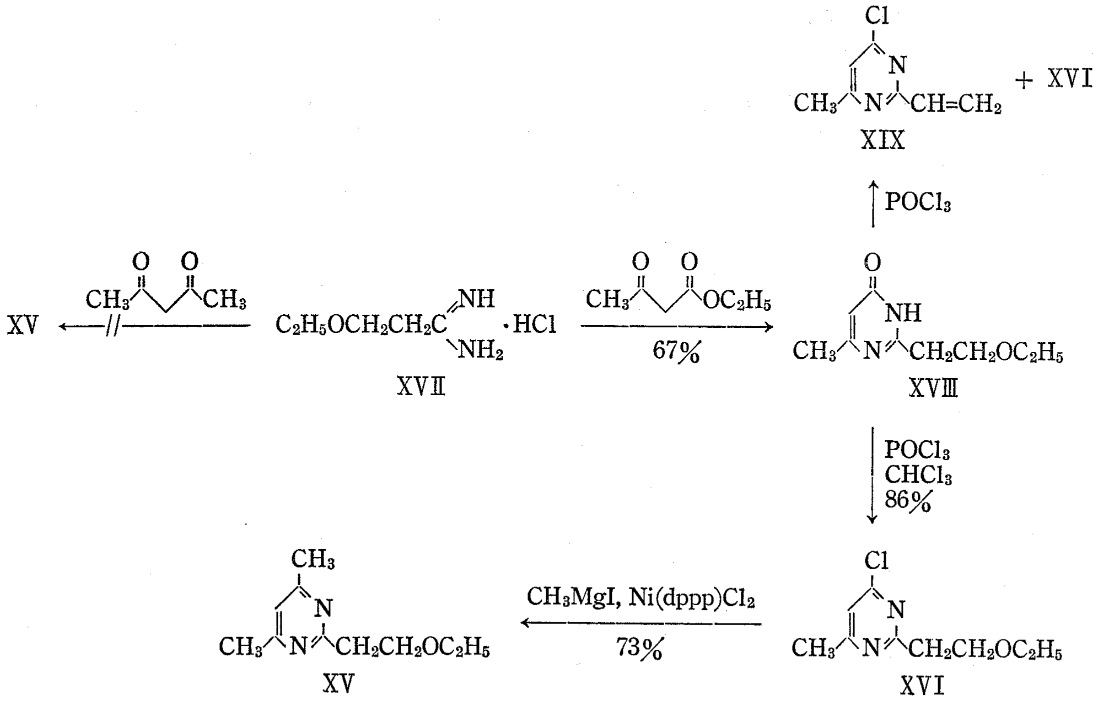

Chart 3

When XVIII was refluxed in phosphoryl chloride without using chloroform, 28% yield of 4-chloro-6-methyl-2-vinylpyrimidine (XIX) was obtained together with a small amount of XVI. Although the preparation of simple 2-vinylpyrimidines has not yet been reported by usual ring closure reactions, this observation suggested the β-ethoxyethyl group being a useful vinyl-protecting group.

The details of vinylpyrimidine synthesis will be mentioned in a subsequent paper.

Experimental[9]

Materials——Nickelphosphine complexes, Ni(dppe)Cl_2 and Ni (dppp)Cl_2 were prepared by the method reported by van Hecke *et al.*[10] The following chloropyrimidines usd as starting materials were synthesized by the reaction of phosphoryl chloride on the corresponding pyrimidinones according to the manner reported on the literatures: 2-chloro-4,6-dimethylpyrimidine (III),[11] 4-chloro-2,6-dimethylpyrimidine (V),[12] 4,6-dichloro-2-methylpyrimidime (VIII),[13] 2,4-dichloro-6-methylpyrimidine (X),[14] and 2,4,6-trichloropyrimidine (XIII).[15]

General Prodecure of the Grignard Coupling Reaction with Monochloropyrimidines——To a mixture of Ni(dppe)Cl_2 or Ni(dppp)Cl_2 (0.2 mmol) and alkyl (or aryl) magnesium halide (0.04 mol) in anhydrous ether (30 ml) was added an ethereal solution of monochloropyrimidines (0.02 mol in 50 ml) at a temperature not exceeding to 0° with stirring. Then the reaction mixture was refluxed for 20 hr with vigorous stirring. After the reaction was completed, dil. HCl was added under ice cooling to hydrolyzed the resulting magnesium complex. The aqueous layer was separated, made alkaline with K_2CO_3, and extracted with ether or $CHCl_3$. After drying te extract over K_2CO_3, the solvent was removed by distillation to give a residue. The dark brown residue was purified by distillation under reduced pressure or by alumina column chromatography and subsequent recrystallization. The results of elemental analysis of the products were listed in Table II.

2-Ethyl-4,6-dimethylpyrimidine (IVa)——From Mg (1.1 g, 0.044 g·atom), C_2H_5Br (4.8 g, 0.044 mol), Ni(dppe)Cl_2 (108 mg, 0.21 mmol), and III (2.9 g, 0.02 mol), IVa was obtained according to the general procedure as a colorless liquid, yield 2 g. NMR (CCl_4): 1.28 (3H, t, $J=8.0$ Hz), 2.38 (6H, s), 2.80 (2H, q, $J=8.0$ Hz), 6.71 (1H, s).

2-*n*-Butyl-4,6-dimethylpyrimidine (IVb)——From Mg (1.1 g, 0.044 g·atom), n-C_4H_9Br (6.1 g, 0.044 mol), Ni (dppe)Cl_2 (108 mg, 0.21 mmol), and III (2.9 g, 0.02 mol), IVb was obtained according to the general procedure as a colorless liquid, yield 2.24 g. NMR (CCl_4): 1.95 (3H, t, $J=7.0$ Hz), 1.1—2.1 (4H, m), 2.7—3.1 (2H, m), 2.46 (6H, m), 6.88 (1H, s).

2-*n*-Amyl-4,6-dimethylpyrimidine (IVc)——From Mg (1.1 g, 0.044 g·atom), n-$C_5H_{11}Br$ (6.7 g, 0.44 mol), Ni(dppe)Cl_2 (108 mg, 0.21 mmol), and III (2.9 g, 0.02 mol), IVc was obtained according to the general procedure as a colorless liquid, yield 2.3 g. NMR (CCl_4): 0.9 (3H, t, $J=5.5$ Hz), 1.1—2.0 (6H, m), 2.33 (6H, s), 2.6—2.9 (2H, m), 6.68 (1H, s).

2-*n*-Hexyl-4,6-dimethylpyrimidine (IVd)——From Mg (1.1 g, 0.044 g·atom), n-$C_6H_{13}Br$ (7.3 g, 0.044 mol), Ni(dppe) Cl_2 (108 mg, 0.21 mmol), and III (2.9 g, 0.02 mol), IVd was obtained according to the general pro-

Table II. Analyses of Compounds IVa—d, VIb, c, XIa, b, XIIa, XIVa

No.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IVa	$C_8H_{12}N_2$	70.55	8.88	20.57	70.15	8.88	20.68
IVb	$C_{10}H_{16}N_2$	73.12	9.82	17.06	72.71	9.78	17.17
IVc	$C_{11}H_{18}N_2$	74.11	10.18	15.71	73.67	10.18	15.76
IVd	$C_{12}H_{20}N_2$	74.95	10.48	14.57	74.69	10.37	14.70
VIb	$C_{12}H_{12}N_2$	78.23	6.57	15.21	78.27	6.47	15.46
VIc	$C_{13}H_{14}N_2$	78.75	7.12	14.13	78.65	7.15	13.91
XIa[a]	$C_{15}H_{17}O_7N_5$	47.49	4.52	18.46	47.49	4.52	18.61
XIb	$C_{17}H_{14}N_2$	82.90	5.73	11.37	83.18	5.63	11.78
XII[a]	$C_{15}H_{17}O_7N_5$	47.49	4.52	18.46	47.89	4.43	18.73
XIVa	$C_{10}H_{16}N_2$	73.12	9.82	17.06	72.77	9.76	16.61

a) Picrate.

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9) All melting points are uncorrected.Infrared (IR) spectra measurements were performed with a JASCO IRA-1 spectrometer. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts were expressed ppm downfield from tetramethylsilane (TMS) as intermal standard. The following abbreviations were used. s=singlet, d=doublet, t=triplet, and m=multiplet.

10) G.R. van Hecke and W.D. Horrocks, Jr., *Inorg. Chem.*, **5**, 1968 (1966).

11) S. Angerstein, *Ber.*, 34, 3956 (1901).

12) E. Ochiai and Y. Ito, *Yakugaku Zasshi*, **57**, 579 (1937).

13) H.R. Henze, W.J. Clegg, and C.W. Smart, *J. Org. Chem.*, **17**, 1320 (1952).

14) T. Matsukawa and B. Ohta, *Yakugaku Zasshi*, **70**, 134 (1950).

15) J. Baddiley and A. Tophan, *J. Chem. Soc.*, **1944**, 678.

cedure as a colorless liquid, yield 2.1 g. NMR (CCl_4): 0.7—1.0 (3H, m), 1.1—1.8 (8H, m). 2.35 (6H, s), 2.5—2.9 (2H, m), 6.69 (1H, s).

4,6-Dimethyl-2-phenylpyrimidine (IVe)——From Mg (1.5 g, 0.06 g·atom), C_6H_5Br (6.1 g, 0.04 mol), Ni(dppe)Cl_2 (108 mg, 0.21 mmol) and III (2.9 g, 0.02 mol), IVe was obtained according to the general procedure, as colorless needles (ether–petr·ether), yield 1.8 g.

4-Ethyl-2,6-dimethylpyrimidine (VIa)——From Mg (1.1 g, 0.044 g·atom), C_2H_5Br (4.8 g, 0.044 mol), Ni(dppe)Cl_2 (108 mg, 0.21 mmol), and V (2.9 g, 0.02 mol), VIa was obtained according to the general procedure, as colorless liquid, yield 1.7 g.

2,4-Dimethyl-6-phenylpyrimidine (VIb)——From Mg (1.5 g, 0.06 g·atom), C_6H_5Br (6.1 g, 0.04 mol), Ni(dppe)Cl_2 (1.08 mg, 0.21 mmol), and V (2.9 g, 0.02 mole), IVb was obtained according to the general procedure as a colorless liquid, yield 3 g. NMR ($CDCl_3$): 2.42 (3H, s), 2.64 (3H, s), 2.64 (3H, s), 7.21 (1H, s). 7.3—7.5 (3H, m), 7.9—8.1 (2H, m).

2-Benzyl-4,6-dimethylpyrimidine (IVf)——To a mixture of Ni(dppp)Cl_2 (0.5 g, 0.9 mmol) and $C_6H_5CH_2MgCl$ prepared from Mg (1.6 g, 0.066 g·atom), and $C_6H_5CH_2Cl$ (5.6 g, 0.044 mol) in anhydrous ether (30 ml), an ethereal solution of III (2.9 g, 0.02 mol in 30 ml) was addded at a temperature not exceeding to 0° with vigorous stirring. Then the dark brown reaction mixture was stirred at room temperatuer for 5 days. The reaction mixture was worked up according to the general procedure given for monochloropyrimidine to afford 1.85 g of IVf, as colorless needles (petr. ether).

4-Benzyl-2,6-dimethylpyrimidine (VIc)——To a mixture of Ni(dppp)Cl_2 (0.5 g, 0.9 mmol), and $C_6H_5CH_2MgCl$ prepared from Mg (1.6 g, 0.066 g·atom) and $C_6H_5CH_2Cl$ (5.6 g, 0.44 mol) in anhydrous ether (30 ml), an ethereal solution of V (2.9 g, 0.02 mol in 30 ml) was added at a temperature not exceeding to 0° with vigorous stirring. Then the reaction mixture was treated as in the case of IVf to give 2.15 g of VIc, as colorless needles (petr. ether). NMR ($CDCl_3$): 2.47 (3H, s), 2.67 (3H, s), 4.00 (2H, s), 6.69 (1H, s), 7.23 (5H, s).

Reaction of 4,6-Dichloro-2-methylpyrimidine (VIII) with Equimolecular Anoumt of Methylmagnesium Iodide——To a ethereal solution of Ni(dppp)Cl_2 (108 mg, 0.21 mmol) and CH_3MgI prepared from Mg (0.55 g, 0.023 g·atom) and CH_3I (3.2 g, 0.023 mol) in anhydrous ether (50 ml), an ethereal solution of VIII (3.3 g, 0.02 mol in 30 ml) was added at 0°. The reaction mixture was treated according to the general procedure to give a colorless liquid, bp 60—130° (150 mmHg). Gas–liquid chromatographic analysis (10% SE 30 packed column (1 m) at 60°, N_2 flow rate of 60 ml/min) showed the ratio of IX: V: VIII in the product to be 2: 1: 5.

Reaction of 4,6-Dichloro-2-methylpyrimidine (VIII) with Excess EtMgBr——To an ethereal solution of Ni (dppp)Cl_2 (100 mg, 0.19 mmol) and EtMgBr prepared from Mg (1.2 g, 0.049 g·atom) and EtBr (5.5 g, 0.05 mol) in anhydrous ether (50 ml) and etheral solution of VIII (3.2 g, 0.02 mol in 30 ml) was added at 0°. The reaction mixture was treated according to the general procedure to give 2.6 g of 4,6-diethyl-2-methylpyrimidine (XIa) as a colorless liquid. NMR (CCl_4): 1.28 (6H, t, $J=7.5$ Hz), 2.68 (3H, s), 2.73 (4H, q, $J=7.5$ Hz), 6.84 (1H, s).

2-Methyl-4,6-diphenylpyrimidine (XIb)——A mixture of Ni(dppp)Cl_2 (54 mg, 0.11 mmol), VIII (1.6 g, 0.01 mol) and C_6H_5MgBr (Mg 1.2 g, 0.049 g·atom and C_6H_5Br 5.5 g, 0.035 mol) in anhydrous ether (80 ml) was treated according to the general procedure. The crude product was purified by column chromatography (Al_2O_3–C_6H_6) and subsequent recrystallization from ether–petr. ether to give 1.6 g of XIb as colorless needles. NMR ($CDCl_3$): 2.86 (3H, s), 7.4—7.7 (6H, m), 7.89 (1H, s), 8.0—8.3 (4H, m).

Reaction of 2,4-Dichloro-6-methylpyrimidine (X) with Equimolecular Amount of CH_3MgI——To an ethereal solurion of Ni (dppp)Cl_2 (100 mg, 0.19 mmol) and CH_3MgI prepared from Mg (0.5 g, 0.02 g·atom) and CH_3I (2.9 g, 0.02 mol) in anhydrous ether (50 ml), an ethereal solution of X (2.8 g. 0.017 mol in 30 ml) was added at 0°. The reaction mixture was treated according to the general procedure to give a colorless liquid, bp 60—145° (110 mmHg). Gas–liquid chromatographic analysis (10% SE 30 column (1 m) at 60°, N_2 flow rate of 60 ml/min) showed the ratio of IX: III: V: X in the product to be 3: 3: 1: 20.

Reaction of 2,4-Dichloro-6-methypyrimidine (X) with Excess EtMgBr ——To an ethereal solution of Ni(dppp)Cl_2 (100 mg, 0.19 mmol) and EtMgBr prepared from Mg (1.2,g 0.05 g·atom) and EtBr (5.5 g, 0.05 mol) in anhydrous ether (50 ml) an ethereal solution of X (3.2 g, 0.02 mol in 30 ml) was added at 0°. The reaction mixture was treated according to the general prodecure to give 2.5 g of 2,4-diethyl-6-methyl pyrimidine (XIIa) as a colorless liquid. NMR (CCl_4): 1.28 (3H, t, $J=7.5$ Hz), 1.34 (3H, t, $J=7.5$ Hz), 2.75 (2H, q, $J=7.5$ Hz), 2.95 (2H, q, $J=7.5$ Hz), 6.92 (1H, s).

4-Methyl-2,6-diphenylpyrimidine (XIIb)——A mixture of Ni(dppp)Cl_2 (50 mg, 0.09 mmol), X (1.6 g, 0.01 mol) and C_6H_5MgBr (Mg 1.2 g, 0.49 g·atom and C_6H_5Br 5.5 g, 0.035 mol) in anhydrous ether (80 ml) was treated according to the general procedure. The crude product was purified by column chromatography (Al_2O_3–C_6H_6) and subsequent recrystallization from ether–petr. ether to give 1.62 g of XXb as colorless needles.

2,4,6-Triethylpyrimidine (XIVa)——A mixture of Ni(dppp)Cl_2 (50 mg, 0.09 mmol), XIII (1.8 g, 0.01mol) and C_2H_5MgBr (Mg 1.3 g, 0.05 g·atom and C_2H_5Br 6.0 g, 0.05 mol) in anhydrous ether (80 ml) was treated according to the general procedure. The crude product was distilled under reduced pressure to give 0.65 g. of XIVa as a colorless liquid. NMR (CCl_4): 1.1—1.5 (9H, m), 2.3—3.2 (6H, m), 6.91 (1H, s).

2,4,6-Triphenylpyrimidine (XIVb)——The mixture of Ni (dppp)Cl_2 (50 mg, 0.09 mmol), XIII (1.5 g, 0.008 mol) and C_6H_5MgBr (Mg 1.3 g, 0.05 g·atom and C_6H_5Br 6.5 g, 0.04 mol) in anhydrous ether (80 ml) was treated according to the general procedure. The crude brown solid was purified by column chromatography (Al_2O_3–ether) and subsequent recrystallization from ether–petr. ether to give 1.4 g of IXc as colorless needles.

2-(β-Ethoxyethyl)-6-methyl-4-pyrimidinone (XVIII)——To a solution of NaOMe–MeOH prepared from metallic sodium (4.6 g, 0.2 g·atom) and abs. MeOH (100 ml) was added XVII (15.25 g, 0.1 mol) and ethyl acetoacetate (13 g, 0.1 mol). The mixture was stirred for 3 hr at room temperature and concentrated under reduced pressure. The residual half solid was dried over in a desiccator over conc. H_2SO_4 under reduced pressure for 2 days. The crude product was dissolved in H_2O, acidified with 3 N HCl and washed with ether. The aqueous phase was neutralized with solid K_2CO_3 and concentrated to dryness under reduced pressure. The solid was extracted with hot AcOEt and the extract sried over K_2CO_3. The solvent was removed and the residue was recrystallized from petr. ether to give colorless needles, mp 125—127°,[16] yield 12.26 g (67.3%).

4-Chloro-2-(β-ethoxyethyl)-6-methylpyrimidine (XVI)——A mixture of XVIII (10.9 g, 0.06 mol), $POCl_3$ (11 ml, 0.12 mol) and $CHCl_3$ (120 ml) was refluxed for 3 hr. The $POCl_3$ and $CHCl_3$ was removed under reduced pressure. The residue was poured into cold NH_4OH and extracted with ether. The solvent was removed and the residue was distilled under reduced pressure to give a colorless liquid, bp 129—135° (22 mmHg), yield 10.35 g (86.0%). NMR (CCl_4): 1.13 (3H, t, J=7.0 Hz), 2.43 (3H, s), 3.07 (2H, t, J=7.0 Hz), 3.45 (2H, q, J=7 Hz), 3.81 (2H, t, J=7.0 Hz), 6.98 (1H, s). *Anal.* Calcd. for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; Cl, 17.67; N, 13.96. Found: C, 54.15; H, 6.58; Cl, 17.60; N, 14.17.

4,6-Dimethyl-2-(β-ethoxyethyl)pyrimidine (XV)——From Mg (0.73 g, 0.032 g·atom), CH_3I (4.26 g, 0.03 mol), Ni(dppp)Cl_2 (0.03 g, 0.055 mmol) and XVI (3.1 g, 0.0154 mol), XV was obtained according to the general procedure of the Grignard coupling reaction as a colorless liquid, bp 120—122° (20.5 mmHg), yield 2.01 g (72.5%). NMR (CCl_4): 1.12 (3H, t, J=7.0 Hz), 2.37 (6H, s), 2.98 (2H, t, J=7,0 Hz), 3.44 (2H, q, J=7 Hz), 3.78 (2H, t, J=7.0 Hz), 6.72 (1H, s). *Anal.* Calcd. for $C_{10}H_{16}N_2O$: C, 66.93; H, 8.95; N, 15.54. Found: C, 65.90; H, 8.98; N, 15.36.

Reaction of XVIII with Phosphoryl Chloride——A mixture of XVIII (3.6 g, 0.02 mol) and $POCl_3$ (50 ml) was refluxed for 4 hr. The excess $POCl_3$ was removed under reduced pressure and the residue was poured into cold NH_4OH. The aqueous phase was extracted with ether and the ethereal solution was dried over K_2CO_3. The ether was removed in the presence of a samll amount of *t*-butylphenol as a stabilizer and the residue was distilled under reduced pressure to give a colorless liquid (XIX), bp 67° (5 mmHg), yield 0.85 g (27.5%) and a colorless liquid (XVI), bp 72—82° (5 mmHg). *Anal.* Calcd. for $C_7H_7ClN_2$ (XIX): C, 54.8; H, 4.56; N, 18.12. Found: C, 54.53; H, 5.33; N, 17.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 990. NMR ($CDCl_3$): 2.50 (3H, s), 5.76 (1H, $AB\underline{X}$), 6.67 (1H, $\underline{A}BX$), 6.77 (1H, $A\underline{B}X$), (the coupling constants of the ABX: J_{AX}=12.4 Hz, J_{BX}=0.4 Hz, J_{AX}=17.25 Hz), 7.04 (1H, s.)

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