Studies on Pyrimidine Derivatives. IX.¹⁾ Coupling Reaction of Mono-substituted Acetylenes with Iodopyrimidines²⁾

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The pyrimidine derivatives containing an acetylenic side chain were synthesized by means of the reaction of alkyl-(or phenyl)acetylenes with twelve kinds of 2-, 4-, and 5-iodopyrimidines in the presence of a palladium triphenylphosphine complex in satisfactory yields. When propargyl alcohol was used, the reaction exhibited the tendency of decreasing the yield.

The reaction readily proceeded in both 2,4-diiodo- and 4,6-diiodo-pyrimidines to give the corresponding dialkynyl derivatives. This acetylene coupling reaction was applicable to the synthesis of the 4-quinazoline derivatives.

Keywords—palladium phosphine complex; iodopyrimidine; alkynylpyrimidine; bispyrimidinylacetylene; 4-alkynylquinazoline; phenethylpyrimidine

In the preceding paper⁴⁾ of this series, we have reported that the coupling reaction of simple halopyrimidines with Grignard reagents is facilitated by the catalytic action of nickel phosphine complexes to give alkylpyrimidines in good yield. This result promoted us to investigate the carbon-carbon bond forming reaction on simple halopyrimidines with the aid of transition metal complexes. In this paper, we wish to report the coupling reaction of mono-substituted acetylenes with various iodopyrimidines.

Recently, Sonogashira *et al.*⁵⁾ described that iodobenzene was readily coupled with mono-substituted acetylenes by adding a catalytic amount of palladium triphenylphosphine complex and cuprous iodide to afford 1-alkyl(or aryl)-2-phenylacetylenes in excellent yield. Since no work on the preparation of pyrimidine derivatives with an acetylenic side chain at the 2- or 4-positions has been reported, the application of this method would be expected to open a way to a simple procedure for the synthesis of these pyrimidines.

At first the fitness of halogen atoms to this reaction was tested on a series of 4,6-dimethyl-2-halopyrimidines. Namely, 2-chloro-, 2-bromo- and 2-iodo-4,6-dimethylpyrimidine (Ia) were treated with an equimolecular amount of phenylacetylene in the presence of a palladium triphenylphosphine complex and cuprous iodide in triethylamine at room temperature for 30 hours giving 4, 6-dimethyl-2-phenylethynylpyrimidine (IIIa) in 5%, 37% and 95% yield, respectively. Hydrogenation of IIIa over palladium charcoal gave 4,6-dimethyl-2-phenethylpyrimidine (Va). The spectral data of IIIa are consistent with its acetylenic structure. Accordingly, among these three 4,6-dimethyl-2-halopyrimidines, the iodide (Ia) was concluded to be the most suitable starting material. Further, 2-iodo- and 4-iodo-pyrimidines are known⁶⁾ to be obtainable from the corresponding chloropyrimidines by treatment with concentrated hydroiodic acid.

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Chart 1

TABLE I. Reaction of 2-Iodopyrimidines with RC≡CH

No.	R ₄	R ₆	R	Yield (%)	mp (°C)	bp (mmHg) (°C)	IR ν_{CHCH} cm ⁻¹	Formula	Analysis (%)		
									Calcd.	(Found)	
									C	H	N
IIIa	CH ₃	CH ₃	C ₆ H ₅	95	87—88	160 (3)	2210	C ₁₄ H ₁₂ N ₂	80.74 (80.81)	5.81 5.89	13.45 13.18
IIIb	CH ₃	CH ₃	CH ₃	80	105—106	140 (18)	2255	C ₉ H ₁₀ N ₂	73.94 (73.44)	6.90 6.90	19.16 19.12
IIIc	CH ₃	CH ₃	n-C ₄ H ₉	70	—	135 (3)	2240	C ₁₂ H ₁₆ N ₂	76.55 (76.44)	8.57 8.61	14.88 14.90
IIId	CH ₃	CH ₃	n-C ₅ H ₁₁	92	—	125 (3)	2250	C ₁₃ H ₁₈ N ₂	77.18 (76.69)	8.97 9.14	13.85 13.52
IIIe	CH ₃	CH ₃	n-C ₁₄ H ₂₉	77	49—50.5	190 (1)	2240	C ₂₂ H ₃₆ N ₂	80.43 (80.23)	11.05 11.25	8.53 8.27
IIIf	H	H	C ₆ H ₅	93	84—85	145 (3)	2230	C ₁₂ H ₈ N ₂	79.98 (79.82)	4.48 4.48	15.55 15.55
IIIg	H	H	n-C ₄ H ₉	86	—	125 (3)	2240	C ₁₆ H ₁₅ N ₅ O ₇ ^{a)}	49.36 (48.68)	3.88 3.74	17.99 17.72
IIIh	OCH ₃	CH ₃	C ₆ H ₅	70	64—65	155 (3)	2235	C ₁₃ H ₁₂ N ₂ O	74.99 (75.13)	5.38 5.46	12.49 12.38
IIIi	OCH ₃	CH ₃	CH ₃	89	52—53	140 (18)	2255	C ₉ H ₁₀ N ₂ O	66.65 (66.78)	6.22 6.26	17.27 17.46
IIIj	OCH ₃	CH ₃	n-C ₄ H ₉	98	—	135 (3)	2240	C ₁₂ H ₁₆ N ₂ O	70.56 (70.24)	7.90 7.99	13.72 13.50
IIIk	N	CH ₃	C ₆ H ₅	66	89—90	180 (3)	2220	C ₁₈ H ₁₉ N ₃	77.94 (78.17)	6.91 6.99	15.51 15.07
IIIl	N	CH ₃	CH ₃	98	—	140 (18)	2255	C ₁₉ H ₂₀ N ₆ O ₇ ^{b)}	51.35 (51.35)	4.54 4.43	18.91 18.84
III m	N	CH ₃	n-C ₄ H ₉	83	—	165 (3)	2240	C ₁₆ H ₂₃ N ₃	74.66 (75.10)	9.01 9.08	16.33 16.25

a) Picrate, mp 75—76°. b) Picrate, mp 152—154°.

TABLE II. Reaction of 4-Iodopyrimidines with R-C≡CH

No.	R ₄	R ₆	R	Yield (%)	mp (°C)	bp (mmHg) (°C)	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm ⁻¹ -C≡C-	Formula	Analysis (%) Calcd. (Found)		
									C	H	N
IVa	CH ₃	CH ₃	C ₆ H ₅	84	82—83.5	165 (3)	2220	C ₁₄ H ₁₂ N ₂	80.74 (80.49)	5.81 5.78	13.45 13.51
IVb	CH ₃	CH ₃	CH ₃	80	58—60	110 (3)	2240	C ₉ H ₁₀ N ₂	73.94 (73.68)	6.90 7.00	19.16 19.10
IVc	CH ₃	CH ₃	n-C ₄ H ₉	86	—	125 (3)	2240	C ₁₂ H ₁₆ N ₂	76.55 (76.67)	8.57 8.50	14.88 14.60
IVd	CH ₃	CH ₃	n-C ₅ H ₁₁	83	—	130 (3)	2240	C ₁₃ H ₁₈ N ₂	77.88 (76.95)	8.97 9.19	13.85 13.67
IVe	CH ₃	CH ₃	n-C ₁₄ H ₂₉	73	—	200 (1)	2235	C ₂₂ H ₃₆ N ₂	80.43 (80.38)	11.05 10.75	8.53 8.35
IVf	iso-C ₃ H ₇	CH ₃	C ₆ H ₅	98	—	175—177 (3)	2240	C ₁₆ H ₁₆ N ₂	81.32 (81.57)	6.83 6.98	11.86 11.35
IVg	iso-C ₃ H ₇	CH ₃	CH ₃	93	—	118 (18)	2255	C ₁₁ H ₁₄ N ₂	75.82 (75.77)	8.10 8.06	16.08 15.96
IVh	iso-C ₃ H ₇	CH ₃	n-C ₄ H ₉	98	—	130 (3)	2240	C ₁₄ H ₂₀ N ₂	77.73 (77.93)	9.32 9.49	12.95 12.96
IVi	iso-C ₃ H ₇	CH ₃	n-C ₅ H ₁₁	93	—	127 (3)	2245	C ₁₆ H ₂₂ N ₂	78.21 (78.05)	9.63 9.89	12.16 12.17
IVj	iso-C ₃ H ₇	CH ₃	n-C ₁₄ H ₂₉	93	—	210 (3)	2240	C ₂₄ H ₄₀ N ₂	80.83 (80.41)	11.31 11.45	7.83 7.67
IVk	OC ₆ H ₅	CH ₃	C ₆ H ₅	55	138—139.5	220 (3)	2240	C ₁₉ H ₁₄ N ₂	84.82 (84.67)	5.22 5.13	10.36 10.27
IVl	C ₆ H ₅	CH ₃	n-C ₄ H ₉	98	—	170—175 (3)	2240	C ₁₇ H ₁₈ N ₂	81.56 (81.51)	7.25 7.25	11.19 11.32
IVm	OCH ₃	OCH ₃	C ₆ H ₅	80	166—168	—	2220	C ₁₄ H ₁₂ N ₂ O ₂	69.99 (70.18)	5.03 5.03	11.66 11.47
IVn	OCH ₃	OCH ₃	n-C ₄ H ₉	75	—	160 (3)	2240	C ₁₂ H ₁₆ N ₂ O ₂	65.43 (64.95)	7.32 7.32	12.72 13.32
IVo	SCH ₃	CH ₃	C ₆ H ₅	92	73—74.5	190 (3)	2215	C ₁₄ H ₁₂ N ₂ S	69.99 (70.29)	5.03 4.97	11.66 11.47
IVp	SCH ₃	CH ₃	CH ₃	80	76—77	120 (3)	2260	C ₉ H ₁₀ N ₂ S	60.66 (60.75)	5.66 5.95	15.72 15.94
IVq	SCH ₃	CH ₃	n-C ₄ H ₉	94	—	165 (3)	2240	C ₁₂ H ₁₆ N ₂ S	65.43 (65.17)	7.32 7.24	12.72 12.26
IVr	SCH ₃	CH ₃	n-C ₅ H ₁₁	80	—	155—160 (3)	2240	C ₁₃ H ₁₈ N ₂ S	66.64 (66.35)	7.74 7.80	11.96 12.35

Thus, the coupling reaction was studied on nine kinds of iodopyrimidines (Ia—d and IIa—e) according to the same manner given for Ia. As shown in Table I (2-iodopyrimidines) and Table II (4-iodopyrimidines), the results were satisfactory. The presence of methoxyl, methylthio, and 1-piperidinyl groups on the ring, did not inhibit this coupling reaction.

Concerning with the reaction path way of this coupling, it was observed that IIa did not react with triethylamine at room temperature. This demonstrates a triethyl pyrimidinyl-ammonium salt not to be a reaction intermediate.⁷⁾

Comparing with 2- or 4-halopyrimidines, 5-halogeno derivatives are well accepted to be unreactive toward nucleophilic reagents. However, 5-halopyrimidines such as 5-bromo-2,4-dimethyl- (VIIa) and 5-iodo-2-isopropyl-4-methyl-pyrimidine (VIIb) readily reacted, as well as the 2- and 4-isomers, with monosubstituted acetylenes under similar conditions, giving the

7) When 2- or 4-iodopyrimidines were allowed to react with trimethylamine instead of triethylamine, the corresponding ammonium iodides were obtained, and these ammonium salts were reported to react with cyanide ion. [W. Klötzer, *Monatsch. Chem.*, **87**, 526 (1956)]. However, the coupling reaction of 4,6-dimethyl-2-pyrimidinyl trimethylammonium chlorides (IX) with phenylacetylene did not afford the product (IIIa) under identical conditions.

corresponding products (VIIIa—d). From a comparison of the results summarized in Table III with that in Table I, II, it may not be seen that in all the cases, there is essential difference due to the reactivity of these halides.

There are few papers⁸⁾ dealing with the facile synthesis of the 5-ethynypyrimidine derivatives. For instance, 5-acetyl-4-methyl-2-phenylpyrimidine (X) was converted to 5-ethynyl-4-methyl-2-phenylpyrimidine in poor yield by treatment X with phosphorous pentachloride and subsequent dehydrochlorination. Therefore, the coupling reaction at the 5-position may provide a convenient method for the synthesis of the 5-acetylenic compounds.

Although the reaction of propiolic acid with iodopyrimidines failed to give a significant product, propargyl alcohol was coupled with 2-,4-, and 5-iodopyrimidines (Table IV).

When acetylene gas was blown through a warm solution of IIa in triethylamine, colorless needles ($C_{14}H_{14}N_4$, MS: $m/e=238$, mp 153—154°) (XIa) was obtained in 37% yield. In the infrared spectrum of XIa no absorption band was observed at 2200 cm^{-1} region, and the nuclear magnetic resonance spectrum of XIa shows three singlets at 2.51, 2.71, and 7.23 ppm with the ratio of areal intensity 3:3:1. On the bases of these spectra data, which suggest the structure of the product to be highly symmetric, 1,2-bis(2,6-dimethyl-4-pyrimidinyl) acetylene structure was proposed to XIa. The same result was obtained on the reaction of IIb to give 1,2-bis(2-isopropyl-6-methyl-4-pyrimidinyl) acetylene (XIb), mp 60.5—62.0° in 58% yield.

Furthermore, in the case of 2,4-diiodo-6-methyl- (XII) or 4,6-diiodo-2-methyl-pyrimidine (XIII), the reaction with monoalkylacetylenes gave rise to the diacetylenic compounds (XIV and XV). Based on the results of the experiments described above, the stepwise coupling seemed to be difficult.

In order to extend this coupling reaction to a pyrimidine benzologue, 4-chloroquinazoline (XVI) was tested to react with phenylacetylene. While 4-iodoquinazoline (XVII) was not

TABLE III. Reaction of 5-Halopyrimidines with $RC\equiv CH$

No.	R_2	R_4	R	Yield (%)	mp (°C)	bp (mmHg) (°C)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} $-C\equiv C-$	Formula	Analysis (%)		
									Calcd.	(Found)	N
VIIIa	CH_3	CH_3	C_6H_5	42	113—114.5	180(3)	2235	$C_{14}H_{12}N_2$	80.74 (80.54)	5.81 5.88	13.45 13.40
VIIIb	$iso-C_3H_7$	CH_3	C_6H_5	93	53	155(1)	2225	$C_{16}H_{16}N_2$	81.32 (81.41)	6.93 6.83	11.86 11.85
VIIIc	$iso-C_3H_7$	CH_3	$n-C_4H_9$	93	—	140—143 (3)	2235	$C_{14}H_{20}N_2$	77.73 (77.80)	9.32 9.39	12.95 12.44
VIII d	OCH_3	OCH_3	C_6H_5	53	68—70	180(2)	2230	$C_{14}H_{12}N_2O_2$	69.99 (69.87)	5.03 4.93	11.66 11.66

8) R. Hull, *J. Chem. Soc.*, 1958, 3742.

TABLE IV. Reaction of Iodopyrimidines with Propargyl Alcohol

No.	Yield (%)	mp (°C)	bp (mmHg) (°C)	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}		Formula	Analysis (%)		
				—OH	—C $\equiv$ C—		Calcd.	(Found)	
							C	H	N
III _n	56	155—157	—	3620 3400	2250	C ₉ H ₁₀ N ₂ O	66.65 (66.74)	6.22 6.00	17.27 17.14
III _o	34	158.5—160	—	3635 3300	2260	C ₉ H ₁₀ N ₂ O ₂	60.66 (60.37)	5.66 5.60	15.72 15.45
IV _s	37	121.5—123	—	3300	2240	C ₉ H ₁₀ N ₂ O	66.65 (67.15)	6.22 6.07	17.27 17.67
IV _t	47	—	145(2)	3630 3350	2255	C ₁₁ H ₁₄ N ₂ O	69.44 (69.00)	7.42 7.49	14.73 14.38
IV _u	66	102—103.5	—	3620 3350	2240	C ₉ H ₁₀ N ₂ OS	55.66 (55.85)	5.19 5.23	14.43 14.09
VIII _f	57	—	155(1)	3635 3240	—	C ₁₁ H ₁₄ N ₂ O	69.44 (69.21)	7.42 7.45	14.73 14.86

Chart 3

obtained through the reaction of XVI with potassium iodide, XVI was observed to have enough reactivity for the coupling reaction to give the corresponding acetylenic derivatives (XVIIIa,b) in considerable yield. Since quinazoline derivatives are reported to have excellent reactivity toward nucleophiles at the 4-positions,⁹⁾ the results listed in Table V might be reasonable.

Chart 4

TABLE V. Reaction of 4-Chloroquinazoline with $\text{RC}\equiv\text{CH}$

No.	R	Yield (%)	mp (°C)	bp (mmHg) (°C)	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} —C≡C—	Formula	Analysis (%)		
							Calcd.	(Found)	
							C	H	N
XVIIIa	C ₆ H ₅	44	66—67	175—180 (3)	2220	C ₁₆ H ₁₀ N ₂	83.45 (83.57)	4.38 4.35	12.17 11.93
XVIIIb	<i>n</i> -C ₄ H ₉	44	—	153 (3)	2220	C ₁₄ H ₁₄ N ₂	79.96 (79.85)	6.71 7.15	13.32 13.51

9) T. Higashino, *Yakugaku Zasshi*, **80**, 1404 (1960).

In conclusion, the acetylenic coupling reaction devised for iodobenzene⁵⁾ is of wide application for introducing the acetylenic side chain in pyrimidine and quinazoline rings.

Experimental⁹⁾

Bis(triphenylphosphine)palladium dichloride [Pd(PPh₃)₂Cl₂] was prepared according to the method by Burmeister *et al.*¹⁰⁾ The following halopyrimidines and chloroquinazoline were prepared by known methods: 2-chloro-4,6-dimethyl-,¹¹⁾ 2-bromo-4,6-dimethyl-,¹²⁾ 2-iodo- (Ia),¹³⁾ 2-iodo-4,6-dimethyl- (Ib),^{6a)} 4-iodo-2,6-dimethyl- (IIa),^{6a)} 4-iodo-6-methyl-2-phenyl- (IIc),^{6a)} 4-iodo-2,6-dimethoxy- (IId),¹⁴⁾ 4-iodo-6-methyl-2-methylthio- (IIe),^{6a)} 5-iodo-2,4-dimethoxy- (VIIc),¹⁵⁾ 2,4-diiodo-6-methyl-pyrimidine (XII),^{6b)} and 4-chloro-quinazoline (XVI).¹⁶⁾

Acetylenes: Phenylacetylene, 1-hexyne, 1-heptyne, propargyl alcohol and acetylene were commercially available. 1-Hexadecyne¹⁷⁾ and propyne¹⁸⁾ were also prepared by known procedures.

Synthesis of Iodopyrimidines from Chloropyrimidines—2-Iodo-4-methoxy-6-methyl- (Ic), 2-iodo-4-methyl-6-piperidino- (Id), 4-iodo-2-isopropyl-6-methyl- (IIb), and 4,6-diiodo-2-methyl-pyrimidine (XIII) were synthesized by the following procedure: A chloropyrimidine (or dichloropyrimidine) (10 g) was occasionally shaken at room temperature with 57% hydroiodic acid (50 ml) for 2 days. The crude precipitate were collected by filtration and dissolved in water. The resulting solution was made alkaline with potassium carbonate and extracted with benzene (or chloroform). The benzene (or chloroform) layer was washed with aqueous sodium sulfite and dried over anhydrous potassium carbonate. After removal of the solvent, the crude iodopyrimidine (or diiodopyrimidine) was purified by distillation under reduced pressure or recrystallization. The results of elemental analysis and physical constants of the resulting iodides were listed in Table VI.

TABLE VI. Reaction of Chloropyrimidines with Hydroiodic Acid

No.	Yield (%)	mp (°C) (Recrystal. solvent)	bp (mmHg) (°C)	Formula	Analysis (%)		
					Calcd.	(Found)	
					C	H	N
Ic	61	74—75 (<i>n</i> -hexane)	137—140 (18)	C ₆ H ₇ IN ₂ O	28.82 (29.03)	2.82 2.76	11.20 11.22)
Id	42	111.5—113 (<i>n</i> -hexane)	—	C ₁₀ H ₁₄ IN ₃	39.62 (39.84)	4.66 4.65	13.86 13.97)
IIb	65	—	135(18)	C ₈ H ₁₁ IN ₂	36.66 (36.80)	4.23 4.30	10.68 11.16)
XIII	55	195—197 (CHCl ₃)	—	C ₅ H ₄ I ₂ N ₂	17.36 (17.67)	1.16 1.10	8.10 8.37)

5-Bromo-4-hydrazino-2,6-dimethylpyrimidine—5-Bromo-4-chloro-2,4-dimethylpyrimidine¹⁹⁾ (4.3 g, 0.02 mol) was refluxed in a solution of 90% hydrazine hydrate (10 ml) and ethanol (100 ml) for 1 hr. The solution was concentrated under reduced pressure to give the precipitate which was the almost pure hydrazino-pyrimidine. Yield was quantitative and the crude material was used in the next step. The analytical sample was purified by recrystallization from EtOH, mp 145—146°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3260, 3160. NMR (CDCl₃): 2.37 (3H, s), 2.39 (3H, s), 3.50—4.70 (2H, broad), 7.80—8.50 (1H, s). Anal. Calcd. for C₆H₉BrN₄: C, 33.20; H, 4.18; N, 25.81. Found: C, 32.82; H, 4.05; N, 25.88.

- 9) All melting points were uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts were expressed by ppm downfield from TMS as internal standard. The following abbreviations were used: s=singlet, d=doublet, t=triplet, and m=multiplet.
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5-Bromo-2,4-dimethylpyrimidine (VIIa)—The crude 5-bromo-4-hydrazino-2,6-dimethylpyrimidine (13.7 g, 0.063 mol) was refluxed with silver acetate (27.0 g, 0.16 mol) in water (45 ml) for 2 hr. After the resulting precipitates were filtered off, the filtrate was made alkaline with potassium carbonate and extracted with ether. The ether layer was dried over anhydrous potassium carbonate and concentrated to give the residue which was distilled under reduced pressure, bp 78–81° (18 mmHg), mp 41–42°. Yield 7.9 g (67%). NMR (CDCl₃): 2.63 (3H, s), 2.69 (3H, s), 8.72 (1H, s). *Anal.* Calcd. for C₆H₇BrN₂: C, 38.53; H, 3.77; N, 14.98. Found: C, 38.31; H, 3.55; N, 14.59.

5-Iodo-2-isopropyl-6-methyl-4(3H)-pyrimidinone—2-Isopropyl-6-methyl-4(3H)-pyrimidinone (30.4 g, 0.2 mol) was dissolved in water (150 ml) containing sodium hydroxide (10 g, 0.25 mol). To this solution was then added pulverized iodine (51 g, 0.2 mol) with stirring. After all the iodine had been added the solution was warmed on the steam bath. The precipitate was filtered off, dried, and recrystallized from EtOH to give the iodopyrimidinone, mp 185–186°. Yield 47 g (86%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1655. NMR (CDCl₃): 1.36 (6H, d, *J* = 7.0 Hz), 2.65 (3H, s), 2.60–3.30 (1H, m), 12.00–14.00 (1H, broad). *Anal.* Calcd. for C₈H₁₁IN₂O: C, 34.55; H, 4.00; N, 10.07. Found: C, 34.24; H, 3.83; N, 9.82.

4-Chloro-5-iodo-2-isopropyl-6-methylpyrimidine—A mixture of 5-iodo-2-isopropyl-6-methyl-4(3H)-pyrimidinone (30 g, 0.108 mol) and phosphoryl chloride (300 ml) was refluxed for 1 hr. The excess phosphoryl chloride was evaporated under diminished pressure. The residue was dissolved in benzene, poured into ice-water and the resulting mixture was made alkaline with potassium carbonate and extracted with benzene. The benzene layer was dried over anhydrous potassium carbonate. After removal of the benzene, the residue was distilled under reduced pressure to give the chloropyrimidine, bp 118° (3 mmHg). Yield 30 g (94%). NMR (CDCl₃): 1.31 (6H, d, *J* = 7.5 Hz), 2.79 (3H, s), 2.80–3.50 (1H, m). *Anal.* Calcd. for C₈H₁₁ClIN₂: C, 32.40; H, 3.40; N, 9.45. Found: C, 32.33; H, 3.46; N, 9.47.

4-Hydrazino-5-iodo-2-isopropyl-6-methylpyrimidine—4-Chloro-5-iodo-2-isopropyl-6-methylpyrimidine (5.0 g, 0.017 mol) was heated in a solution of 90% hydrazine hydrate (8 ml) and EtOH (50 ml) for 1 hr. The mixture was concentrated to one quarter of its original volume under reduced pressure. The resulting precipitate was filtered to yield quantitatively the hydrazinopyrimidine, mp 108–109°, which was used without purification in the next step. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3420. NMR (CDCl₃): 1.30 (6H, d, *J* = 7.0 Hz), 2.60 (3H, s), 2.70–3.30 (1H, m), 3.30–4.00 (2H, broad), 6.00–6.80 (1H, broad). This compound was converted to the N-isopropylidene derivative, mp 92–93° (acetone), by treatment with acetone. *Anal.* Calcd. for C₁₁H₁₇IN₄: C, 39.77; H, 5.16; N, 16.87. Found: C, 39.73; H, 5.27; N, 16.71.

5-Iodo-2-isopropyl-4-methylpyrimidine (VIIb)—The crude 4-hydrazino-5-iodo-2-isopropyl-6-methylpyrimidine (3.6 g, 0.0128 mol) was refluxed with silver acetate (5 g, 0.03 mol) in water (15 ml) for 2 hr. After the resulting precipitates were filtered off, the filtrate was made alkaline with potassium carbonate and extracted with ether. The ether layer was dried over anhydrous potassium carbonate and concentrated to give the residue which was distilled under reduced pressure, bp 125° (18 mmHg). Yield 2.35 g (73%). NMR (CDCl₃): 1.35 (6H, d, *J* = 7.0 Hz), 2.71 (3H, s), 2.80–3.50 (1H, m), 9.00 (1H, s). *Anal.* Calcd. for C₈H₁₁IN₂: C, 36.66; H, 4.23; N, 10.69. Found: C, 37.14; H, 4.43; N, 11.03.

General Procedures of Coupling Reaction—A (Procedure for the Reaction with Phenylacetylene, 1-Hexyne, 1-Heptyne, 1-Hexadecyne, and Propargyl Alcohol): A iodopyrimidine (10 mmol) and an acetylene (12 mmol) were dissolved in trimethylamine (60 ml) with a catalytic amount of Pd(PPh₃)₂Cl₂ (0.1 mmol) and CuI (0.05 mmol). After the mixture had been stirred for several hours in nitrogen atmosphere at room temperature, the reaction mixture was concentrated to dryness under reduced pressure. A proper quantity of water (40–50 ml) was added to the residue and the aqueous layer was extracted with benzene. From the benzene extract the coupling products were obtained by vacuum distillation or recrystallization.

B (Procedure of the Reaction with Propyne): In a three necked flask fitted with dry ice condenser, a iodopyrimidine (10 mmol) was dissolved in triethylamine (60 ml) with a catalytic amount of Pd(PPh₃)₂Cl₂ (0.1 mmol) and CuI (0.05 mmol). Propyne generated from 1,2-dibromopropane (20.2 g, 0.1 mol) with potassium hydroxide (18 g, 0.32 mol) in *n*-butanol (40 ml) was introduced to the reaction mixture with stirring for 4 hr at room temperature. Then, according to the general procedure A, the coupling products were isolated.

C (Procedure for the Reaction with Acetylene Gas): A slow current of acetylene gas was passed through a mixture of a iodopyrimidine (0.015 mol), Pd(PPh₃)₂Cl₂ (0.1 mmol), CuI (0.05 mmol), and triethylamine (60 ml) under nitrogen atmosphere for 5 hr with stirring at room temperature. Then according to the general procedure A, the coupling products were isolated.

1,2-Bis(2,6-dimethyl-4-pyrimidinyl)acetylene (XIa)—From IIa (4.0 g, 0.017 mol), Pd(PPh₃)₂Cl₂ (80 mg), CuI (40 mg), and triethylamine (60 ml), XIa was obtained according to the general procedure C. Recrystallization from petr. ether gave colorless needles, mp 153–154°. Yield 0.75 g (37%). NMR (CDCl₃): 2.51 (6H, s), 2.71 (6H, s), 7.23 (2H, s). *Anal.* Calcd. for C₁₄H₁₄N₄: C, 70.56; H, 5.92; N, 23.51. Found: C, 70.40; H, 6.11; N, 23.89.

1,2-Bis(2-isopropyl-6-methyl-4-pyrimidinyl)acetylene (XIb)—From IIb (4 g, 0.015 mol), Pd(PPh₃)₂Cl₂ (80 mg), CuI (40 mg), and triethylamine (60 ml), XIb was obtained according to the general procedure C. Vacuum distillation gave a colorless solid, bp 180° (3 mmHg), mp 60.5–62°. Yield 1.3 g (58%). NMR

(CDCl₃): 1.35 (12H, d, $J=6.5$ Hz), 2.51 (6H, s), 3.20 (2H, m), 7.23 (1H, s), 7.28 (1H, s). *Anal.* Calcd. for C₁₈H₂₂N₄: C, 73.43; H, 7.53; N, 19.03. Found: C, 73.35; H, 7.66; N, 18.90. MS m/e : 294 (M⁺).

6-Methyl-2,4-bis(phenylethynyl)pyrimidine (XIVa)—From XII (3.5 g, 0.01 mol), Pd(PPh₃)₂Cl₂ (160 mg), CuI (80 mg), triethylamine (60 ml), and phenylacetylene (2.2 g, 0.022 mol), XIVa was obtained according to the general procedure A. Recrystallization from petr. ether gave colorless needles, mp 156—157°. Yield 1.1 g (37%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 2230. NMR (CDCl₃): 2.56 (3H, s), 7.20—7.80 (11H, m). *Anal.* Calcd. for C₂₁H₁₄N₂: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.28; H, 4.81; N, 9.23.

6-Methyl-2,4-di(1-hexynyl)pyrimidine (XIVb)—From XII (3 g, 0.0087 mol), Pd(PPh₃)₂Cl₂ (160 mg), CuI (80 mg), triethylamine (80 ml), and 1-hexyne (1.8 g, 0.022 mol), XIVb was obtained according to the general procedure A. Vacuum distillation gave a pale yellow liquid, bp 175° (3 mmHg). Yield 0.7 g (31%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 2240. NMR (CDCl₃): 0.70—2.00 (18H, m), 2.45 (3H, s), 7.03 (1H, s). *Anal.* Calcd. for C₁₇H₂₂N₂: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.06; H, 8.84; N, 10.65.

2-Methyl-4,6-bis(phenylethynyl)pyrimidine (XVa)—From XIII (3.4 g, 0.01 mol), Pd(PPh₃)₂Cl₂ (160 mg), CuI (80 mg), triethylamine (80 ml), and phenylacetylene (2.4 g, 0.024 mol), XVa was obtained according to the general procedure A. Recrystallization from petr. ether gave colorless needles, mp 131—132°. Yield 1.64 g (55%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 2230. NMR (CDCl₃): 2.71 (3H, s), 7.20—7.70 (11H, m). *Anal.* Calcd. for C₂₁H₁₄N₂: C, 85.69; H, 4.79; N, 9.52. Found: C, 85.26; H, 4.73; N, 9.37.

2-Methyl-4,6-di(1-hexynyl)pyrimidine (XVb)—From XIII (3.0 g, 0.0087 mol), Pd(PPh₃)₂Cl₂ (160 mg), CuI (80 mg), triethylamine (80 ml), and 1-hexyne (1.7 g, 0.021 mol), XVb was obtained according to the general procedure A. Vacuum distillation gave a pale yellow liquid, bp 160° (2 mmHg). Yield 0.9 g (41%). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 2240. NMR (CDCl₃): 0.70—2.60 (18H, m), 2.68 (3H, s), 7.12 (1H, s). *Anal.* Calcd. for C₁₇H₂₂N₂: C, 80.27; H, 8.27; N, 11.01. Found: C, 79.58; H, 8.66; N, 10.78.

Hydrogenation of 4,6-Dimethyl-2-(phenylethynyl)pyrimidine (IIIa)—To a solution of IIIa (1.1 g, 0.0052 mol) in MeOH (15 ml), 5% Pd-charcoal (0.5 g) was added and the mixture was shaken under H₂ stream (1 atm) at room temperature. After H₂ absorption ceased (300 ml) the catalyst was removed by filtration and the solvent was removed from the filtrate under reduced pressure. The residue was distilled under reduced pressure to afford a colorless solid, bp 150° (3 mmHg), mp 58—59°. NMR (CDCl₃): 2.43 (6H, s), 3.13 (4H, s), 6.84 (1H, s), 7.23 (5H, s). *Anal.* Calcd. for C₁₄H₁₆N₂: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.98; H, 7.50; N, 12.94.

Hydrogenation of 2,6-Dimethyl-4-(phenylethynyl)pyrimidine (IVa)—In a similar manner described above, IVa (1.1 g, 0.0052 mol) was hydrogenated. The crude product was purified by vacuum distillation to give a colorless liquid, bp 134—140° (18 mmHg), which was identified with the authentic specimen.²⁰⁾ NMR (CDCl₃): 2.39 (3H, s), 2.67 (3H, s), 2.98 (4H, s), 6.72 (1H, s), 7.19 (5H, s).

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20) H.R. Sullivan and W.T. Caldwell, *J. Am. Chem. Soc.*, **77**, 1559 (1955).