[Chem. Pharm. Bull. 27(1) 193—197 (1979)]

UDC 547.853.3.04 : 547.391.1.04

Studies on Pyrimidine Derivatives. X.[1] Coupling Reaction of 5-Halopyrimidines with Olefinic Compounds in the Presence of Palladium Acetate and Triphenylphosphine

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(Received August 29, 1978)

Ethyl 5-pyrimidineacrylates, 5-pyrimidineacrylonitriles, and 5-styrylpyrimidines with alkyl groups at the 2- and 4-positions were synthesized by means of the coupling reaction of 5-halopyrimidines with olefines in the presence of palladium phosphine complex. According to a similar manner, pyridines, quinolines, and isoquinolines with the same substituents at the β-positions were obtained in good yield.

Keywords——palladium acetate triphenylphosphine complex; *trans*-5-olefinic pyrimidine; *trans*-3-olefinic pyridine; *trans*-3-olefinic quinoline; *trans*-4-olefinic isoquinoline; 4,4′-bipyrimidine

In the previous papers[1,3] of this series, we have reported that 2- and 4-chloropyrimidines reacted with alkyl (or aryl) magnesium halides to introduce an alkyl (or aryl) group into the 2- and 4-positions of a pyrimidine ring, and that iodopyrimidines, regardless of the position of the iodine substituent, coupled with monosubstituted acecylenes in the presence of a palladium phosphine complex to give ethynylpyrimidines. In order to establish the synthetic utilities of halopyrimidines more widely, our interest was focussed on the carbon–carbon double bond formation catalyzed by transition metal complexes. Recently, Heck *et al.*[4] reported that the coupling reaction of iodobenzene and olefines with an electron-withdrawing group was brought about by a catalyst which is a complex of palladium acetate and triphenylphosphine.

In this paper we wish to describe the application of these reaction conditions to the synthesis of 5-olefinic pyrimidines and to that of other N-heteroaromatics possessing an olefinic substituent at their β-positions.

According to the similar manner given for the reaction of iodobenzene with the olefines, 5-iodo-2-isopropyl-4-methylpyrimidine (I)[1] was heated with ethyl acrylate in the presence of a catalytic amount of the palladium triphenylphosphine complex in triethylamine at 130° to afford ethyl 2-isopropyl-4-methyl-5-pyrimidineacrylate (IIa) as a sole product, in 69% yield. In the nuclear magnetic resonance (NMR) spectrum of IIa, the coupling constant owing to the olefinic protons on the side chain was observed to be 17.0 Hz. Thus the *trans* configuration is clearly assigned to the product (IIa).

Similarly, the coupling reaction of acrylonitrile and styrene with I gave rise to *trans*-2-isopropyl-4-methyl-5-pyrimidineacrylonitrile (IIb) and *trans*-2-isopropyl-4-methyl-5-styryl pyrimidine (IIc), respectively. As shown in the experimental section, the spectral data of IIb, c are also consistent with the proposed structure including configuration.

As well as I, 5-bromo-2,4-dimethylpyrimidine (III)[1] was easily coupled with ethyl acrylate and styrene to give ethyl 2,4-dimethyl-5-pyrimidineacrylate (IVa) and 2,4-dimethyl-

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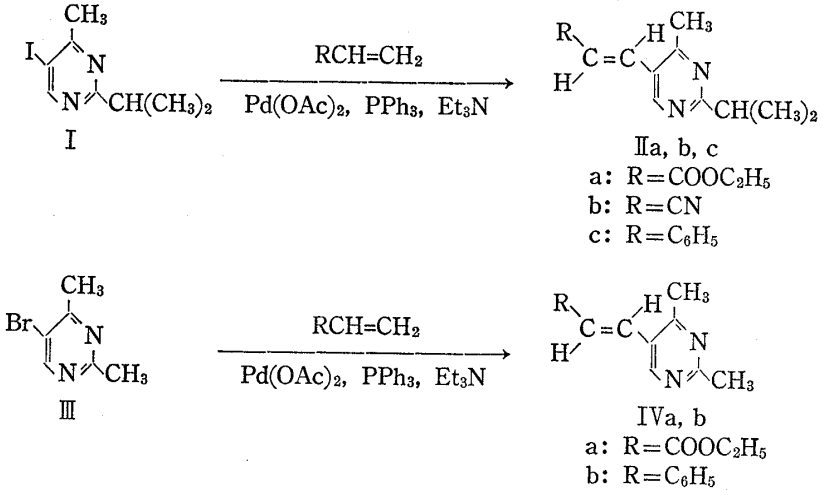


I

IIa, b, c
a: R=$COOC_2H_5$
b: R=CN
c: R=C_6H_5

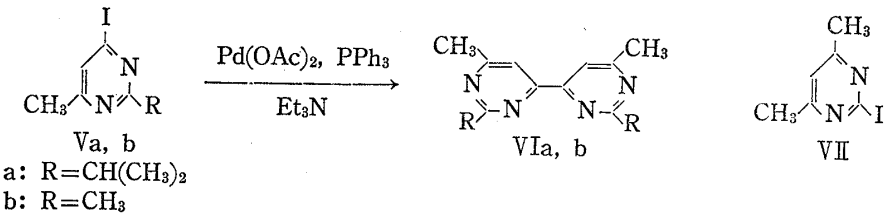
III

IVa, b
a: R=$COOC_2H_5$
b: R=C_6H_5

Chart 1

5-styrylpyrimidine (IVb), respectively. Comparing the yields of the products (IIa, b, c and IVa, b), there seems not much difference in the reactivity of the iodide and the bromide.

The olefinic coupling reaction described above, showed specific affinity to the 5-halopyrimidine, while the acetylenic coupling reaction equally proceeded on 2-, 4-, and 5-iodopyrimidines to give the corresponding products.[1] Namely, when 4-iodo-2-isopropyl-6-methylpyrimidine (Va)[1] was treated with ethyl acrylate under identical conditions (130°), 65% of Va was recovered and no coupling product was obtained. At an elevated temperature (160°), the reaction gave rise to 2,2′-diisopropyl-6,6′-dimethyl-4,4′-bipyrimidine (VIa) in 60% yield, instead of the desired 4-pyrimidineacrylate. The same product (VIa) was obtained in 97% yield by heating Va and the palladium complex in triethylamine at 160° without adding ethyl acrylate. The molecular weight of VIa derived from mass spectrographic data (m/e=270) coincides with the value calculated from the bipyrimidine structure. Similarly, 4-iodo-2, 6-dimethylpyrimidine (Vb)[5] was transformed into 2,2′,6,6′-tetramethyl-4,4′-bipyrimidine (VIb) of which physical constants are in good agreement with those of the authentic specimen reported by McOmie *et al.*[5]



Va, b
a: R=$CH(CH_3)_2$
b: R=CH_3

VIa, b

VII

Chart 2

2-Iodo-4,6-dimethylpyrimidine (VII)[5] seems to be less reactive than Va, b and VII was always recovered when the coupling reaction was performed either with the olefines or without them in the presence of the complex.

Although the coupling reaction of 2- and 4-iodopyrimidines failed to give the pyrimidine derivatives with an ethylenic linkage, the condensation of 2- or 4-methylpyrimidines with aldehydes[6,7] may supplement the defect of this olefinic coupling reaction. On the contrary, there are few papers dealing with the synthesis of 5-olefinic pyrimidines.[8] Accordingly, our

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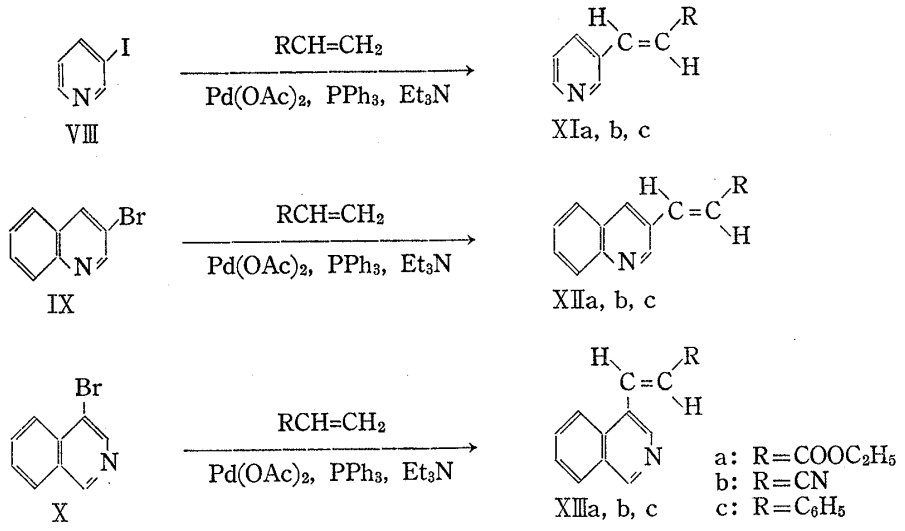

Chart 3

experiments might provide the facile way to the preparation of such 5-substituted pyrimidines.

Finally, in order to extend this reaction to the monoazine series, the coupling of 3-iodopyridine (VIII),[9] 3-bromoquinoline (IX),[10] and 4-bromoisoquinoline (X)[11] with such olefines as ethyl acrylate, acrylonitrile, and styrene was investigated.

As shown in Chart 3 and in the experimental section, three types of ethylenic side chains were well introduced into the β-positions of VIII, IX, and X. The spectral data of all the products (XIa, b, c, XIIa, b, c, and XIIIa, b, c) are in complete agreement with their *trans* olefinic structures. Particularly, infrared (IR) and NMR spectra of ethyl 3-pyridineacrylate (XIa) were identical with those of the authentic specimen reported by Panizzon.[12]

Throughout of this work, it is concluded that, in this coupling reaction, six-membered N-heteroaromatics appear to be specific with respect to iodo (or bromo) substituents at the β-position.

Experimental[13]

General Procedure of Coupling Reaction——A mixture of N-heteroaromatics, olefinic compounds, triethylamine, palladium acetate, and triphenylphosphine was heated in a sealed tube flushed with nitrogen. When the reaction was completed, crystals were precipitated in a sealed tube. The cooled reaction mixture was diluted with water, made alkaline with potassium carbonate, and extracted with benzene. The benzene layer was dried over anhydrous potassium carbonate and concentrated to dryness to give the brown residue which was purified by distillation under reduced pressure or (and) recrystallization. The results of elemental analysis were summerized in Table I.

Ethyl *trans*-2-Isopropyl-4-methyl-5-pyrimidineacrylate (IIa)——A mixture of I (1.3 g, 0.005 mol), ethyl acrylate (0.6 g, 0.006 mol), Et_3N (0.6 g, 0.006 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 120—130° for 1 hr to give a pale yellow liquid, bp 135° (2 mmHg). Yield 0.8 g (69%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 980. NMR ($CDCl_3$): 1.36 (6H, d, J=7.0 Hz), 1.38 (3H, t, J=7.0 Hz), 2.65 (3H, s), 2.90—3.60 (1H, m), 4.36 (2H, q, J=7.0 Hz), 6.52 (1H, d, J=17.0 Hz), 7.97 (1H, d, J=17.0 Hz), 8.90 (1H, s).

***trans*-2-Isopropyl-4-methyl-5-pyrimidineacrylonitrile (IIb)**——A mixture of I (1.3 g, 0.005 mol), acrylonitrile (0.3 g, 0.006 mol), Et_3N (0.6 g, 0.006 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 120-

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10) R.R. Renshaw and H.L. Friedman, *J. Am. Chem. Soc.*, **61**, 3320 (1939).
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13) 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 an internal standard. The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

130° for 2.5 hr to give colorless needles (ether–hexane), mp 87—89°, bp 128—130° (2 mmHg). Yield 0.75 g (81%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2235, 990. NMR ($CDCl_3$): 1.35 (6H, d, J=7.0 Hz), 2.63 (3H, s), 2.90—3.60 (1H, m), 6.00 (1H, d, J=17.5 Hz), 7.70 (1H, d, J=17.5 Hz), 8.82 (1H, s).

***trans*-2-Isopropyl-4-methyl-5-styrylpyrimidine (IIc)**——A mixture of I (2.6 g, 0.01 mol), styrene (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd $(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 150° for 17 hr to give a colorless liquid, bp 180° (2 mmHg). Yield 1.4 g (59%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 975. NMR ($CDCl_3$): 1.36 (6H, d, J=7.0 Hz), 2.59 (3H, s), 2.80—3.70 (1H, m), 7.14 (2H, s), 7.20—7.80 (5H, m), 8.80 (1H, s).

Ethyl *trans*-2,4-Dimethyl-5-pyrimidineacrylate (IVa)——A mixture of III (1.9 g, 0.01 mol), ethyl acrylate (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd $(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 150° for 6 hr to give colorless needles (petr. ether), mp 68—69°, bp 140—145° (2 mmHg). Yield 1.2 g (57%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 990. NMR ($CDCl_3$): 1.36 (3H, t, J=7.5 Hz), 2.66 (3H, s), 2.73 (3H, s), 3.33 (2H, q, J=7.5 Hz), 6.43 (1H, d, J=16.0 Hz), 7.87 (1H, d, J=16.0 Hz), 8.77 (1H, s).

***trans*-2,4-Dimethyl-5-styrylpyrimidine (IVb)**——A mixture of III (1.9 g, 0.01 mol), styrene (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 150° for 16 hr to give colorless needles (ether), mp 80—81°, bp 170° (2 mmHg). Yield 1.6 g (75%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 975. NMR ($CDCl_3$): 2.70 (3H, s), 7.08 (2H, s), 7.20—7.80 (5H, m), 8.73 (1H, s).

Ethyl *trans*-3-Pyridineacrylate (XIa)——A mixture of VIII (2.1 g, 0.01 mol), ethyl acrylate (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 4 hr to give a pale yellow liquid, bp 120° (2 mmHg), which was identical with the authentic specimen.[12] Yield 1.3 g (72%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 985. NMR ($CDCl_3$): 1.35 (3H, t, J=6.5 Hz), 4.35 (2H, q, J=6.5 Hz), 6.58 (1H, d, J=16.5 Hz), 7.30—7.60 (1H, m), 7.80 (1H, d, J=16.5 Hz), 7.80—8.20 (1H, m), 8.60—9.00 (2H, m).

***trans*-3-Pyridineacrylonitrile (XIb)**——A mixture of VIII (2.1 g, 0.01 mol), acrylonitrile (0.7 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 10 hr to give colorless needles (ether), mp 118°. Yield 0.85 g (64%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2235, 980. NMR ($CDCl_3$): 5.99 (1H, d, J=18.0 Hz), 7.45 (1H, d, J=18.0 Hz), 7.20—8.10 (2H, m), 8.60—8.90 (2H, m).

***trans*-3-Styrylpyridine (XIc)**——A mixture of VIII (2.1 g 0.01 mol), styrene (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 4 hr to give colorless needles (benzene–hexane), mp 83—84.5°, bp 160° (2 mmHg). Yield 1.6 g (86%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 970. NMR ($CDCl_3$): 7.20 (2H, s), 7.30—7.80 (6H, m), 7.80—8.10 (1H, m), 8.50—8.70 (1H, m).

Ethyl *trans*-3-Quinolineacrylate (XIIa)——A mixture of IX (2.1 g, 0.01 mol), ethyl acrylate (1.2 g, 0.012 mol), Et_3N (1.2 g, 0.012 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 7 hr to give colorless needles (petr. ether), mp 95.5—97°. Yield 1.65 g (72%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 970. NMR ($CDCl_3$): 1.40 (3H, t, J=7.5 Hz), 4.39 (2H, q, J=7.5 Hz), 6.78 (1H, d, J=16.5 Hz), 8.00 (1H, d, J=16.5 Hz), 7.70—8.30 (4H, m), 8.30—8.50 (1H, m), 9.20—9.40 (1H, m).

***trans*-3-Quinolineacrylonitrile (XIIb)**——A mixture of IX (1.8 g, 0.009 mol), acrylonitrile (0.5 g, 0.01 mol), Et_3N (1.0 g, 0.01 mol), Pd$(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 5 hr to give colorless needles (acetone), mp 151—153°, bp 180° (2 mmHg). Yield 0.65 g (41%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2220, 975. NMR ($CDCl_3$): 6.17 (1H, d, J=17.0 Hz), 7.65 (1H, d, J=17.0 Hz), 7.70—8.60 (5H, m), 9.00—9.30 (1H, m).

***trans*-3-Styrylquinoline (XIIc)**——A mixture of IX (2.1 g, 0.01 mol), styrene (1.3 g, 0.013 mol), Et_3N

Table I. Elemental Analysis of the Ethylenic N-Heteroaromatics

No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	$C_{13}H_{18}N_2O_2$	66.64	7.74	11.96	66.48	7.66	11.99
IIb	$C_{11}H_{13}N_3$	70.56	7.00	22.44	70.78	6.86	22.32
IIc	$C_{16}H_{18}N_2$	80.63	7.61	11.76	80.44	7.61	11.96
IVa	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58	63.90	6.76	13.56
IVb	$C_{14}H_{14}N_2$	79.96	6.71	13.32	79.90	6.73	13.34
XIb	$C_8H_6N_2$	73.83	4.65	21.53	74.07	4.51	21.58
XIc	$C_{13}H_{11}N$	86.16	6.12	7.73	86.16	6.27	7.77
XIIa	$C_{14}H_{13}NO_2$	73.99	5.77	6.16	74.02	5.76	6.17
XIIb	$C_{12}H_8N_2$	79.98	4.48	15.55	80.33	4.67	15.58
XIIc	$C_{17}H_{13}N$	88.28	5.67	6.06	88.35	5.86	6.12
XIIIa	$C_{20}H_{16}N_4O_9$[a]	52.63	3.53	12.28	52.41	3.94	11.85
XIIIb	$C_{12}H_8N_2$	79.98	4.48	15.55	79.45	4.66	15.27
XIIIc	$C_{17}H_{13}N$	88.19	5.67	6.06	88.19	5.85	5.99

a) Picrate, mp 199—200° (acetone).

(1.2 g, 0.012 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 4 hr to give colorless needles (benzene), mp 104—105.5°, bp 200° (2 mmHg). Yield 1.6 g (69%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 965. NMR ($CDCl_3$): 7.32 (2H, s), 7.30—8.10 (8H, m), 8.10—8.30 (2H, m), 9.10—9.40 (1H, m).

Ethyl *trans*-4-Isoquinolineacrylate (XIIIa)——A mixture of X (2.1 g, 0.01 mol), ethyl acrylate (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 150° for 13 hr to give a pale yellow liquid, bp 180° (2 mmHg). Yield 0.9 g (75%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 975. NMR ($CDCl_3$): 1.35 (3H, t, J=7.0 Hz), 4.31 (2H, q, J=7.0 Hz), 6.53 (1H, d, J=16.0 Hz), 7.10—8.10 (4H, m), 8.30 (1H, d, J=16.0 Hz), 8.71 (1H, s), 9.18 (1H, s).

***trans*-4-Isoquinolineacrylonitrile (XIIIb)**——A mixture of X (2.1 g, 0.01 mol), acrylonitrile (0.7 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 150° for 13 hr to give colorless needles (acetone), mp 145—146°, bp 180° (2 mmHg). Yield 0.3 g (18%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2210, 970. NMR ($CDCl_3$): 6.01 (1H, d, J=17.0 Hz), 7.30—8.40 (5H, m), 8.65 (1H, s), 9.30 (1H, s).

***trans*-4-Styrylisoquinoline (XIIIc)**——A mixture of X (2.1 g, 0.01 mol), styrene (1.3 g, 0.013 mol), Et_3N (1.2 g, 0.012 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 140° for 24 hr to give colorless needles (benzene), mp 80—82°, bp 190° (2 mmHg). Yield 1.9 g (81%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 970. NMR ($CDCl_3$): 7.20—8.30 (11H, m), 8.73 (1H, s), 9.13 (1H, s).

2,2′-Diisopropyl-6,6′-dimethyl-4,4′-bipyrimidine (VIa)——i) A mixture of Va (1.3 g, 0.005 mol), ethyl acrylate (0.6 g, 0.006 mol), Et_3N (0.6 g, 0.006 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 160° for 17 hr to give colorless needles (ether), mp 126—128°. Yield 0.4 g (60%). NMR ($CDCl_3$): 1.39 (12H, d, J=7.5 Hz), 2.64 (6H, s), 2.90—3.60 (2H, m), 8.19 (2H, s). MS *m/e*: 270 (M^+). *Anal.* Calcd. for $C_{16}H_{22}N_4$: C, 71.07; H, 8.20; N, 20.73. Found: C, 70.70; H, 8.15; N, 20.82.

ii) A mixture of Va (1.3 g, 0.005 mol), Et_3N (0.6 g, 0.006 mol), $Pd(OAc)_2$ (30 mg), and PPh_3 (60 mg) was heated at 160° for 12 hr to give colorless needles (ether), mp 126—128°, which was identical with the compound obtained by above experiment. Yield 0.65 g (97%).

2,2′,6,6′-Tetramethyl-4,4′-bipyrimidine (VIb)——A mixture of Vb (1.2 g, 0.005 mol), Et_3N (1.0 g, 0.01 mol), $Pd(OAc)_2$ (60 mg), and PPh_3 (120 mg) was heated at 160° for 17 hr. The crude product was purified by alumina column chromatography. From the petr. ether eluate, Vb (0.6 g, 50%) was recovered. The ether eluate gave VIb which was recrystallized from $CHCl_3$–hexane to give colorless needles, mp 158—160° (lit.[5] mp 157—159°). NMR ($CDCl_3$): 2.59 (6H, s), 2.78 (6H, s), 8.09 (2H, s). MS *m/e*: 214 (M^+).

Acknowledgement The authors express their deep gratitude to all the staffs of the Central Analysis Room on this Institute for elemental analysis and measurement of NMR spectra.