Studies on Pyrimidine Derivatives. XLI.[1] Palladium-Catalyzed Cross-Coupling Reaction of Halopyrimidines with Aryl- and Vinyltributylstannanes

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The arylation of 2-, 4-, and 5-halopyrimidines with aryltributylstannanes in the presence of dichlorobis-(triphenylphosphine)palladium was investigated with successful results. The reaction can be expanded to the synthesis of 2-, 4-, and 5-vinylpyrimidines with generality. The site-selectivity of the reaction for 4,5-dihalopyrimidines is also described.

Keywords palladium catalyzed reaction; halopyrimidine; aryltributylstannane; vinyltributylstannane; arylpyrimidine; vinylpyrimidine; site-selectivity

Palladium-catalyzed reactions of aryl halides with various types of carbon reagents are recognized to be most efficient carbon–carbon bond forming methods on aromatic nuclei.[2] Among them, the reaction of aryl halides with aryltrialkylstannanes or tetraarylstannanes to connect an aromatic ring to another one[3-9] seems to be suggestive for the introduction of an olefinic carbon-chain into heteroaromatic nuclei. In fact, the palladium-catalyzed reaction of aryl halides with vinyltributylstannanes was reported recently.[9,10] In the present paper, we describe the palladium-catalyzed reaction of various halopyrimidines with aryl- and vinyltributylstannanes and the site-selectivity of the reaction toward 4,5-dihalopyrimidines for developing the synthesis of aryl- and vinylpyrimidines.

When 2-chloro-4,6-dimethylpyrimidine (**1**) was treated with tributylphenylstannane[11] in the presence of dichlorobis(triphenylphosphine)palladium, 4,6-dimethyl-2-phenylpyrimidine (**2a**) was obtained in satisfactory yield. The palladium-catalyzed reaction of **1** with 2-thienyl-,[12] vinyl-[13] and 2-(trimethylsilyl)vinyltributylstannane[14] gave the corresponding 2-aryl- and 2-vinyl-4,6-dimethylpyrimidines (**2b**–**d**), as expected.

Similarly, 4-chloro-2,6-dimethylpyrimidine (**3**) underwent the palladium-catalyzed reaction with the same stannanes, so that the reaction of 2- and 4-chloropyrimidines was concluded to be effective for the synthesis of pyrimidine derivatives having an aryl or a vinyl substituent at the 2- and 4-positions (so-called active positions).

On the other hand, 5-chloro-2,4-dimethylpyrimidine (**5**), in which the chloro substituent is known to be inactive for nucleophilic substitution, did not react with these stannane derivatives. When 5-iodo-2,4-dimethylpyrimidine (**7**) was employed as a substrate instead of **5**, the reaction proceeded smoothly to give 5-substituted 2,4-dimethylpyrimidines (**8a**–**d**) in considerable yields. Judging from the yield of

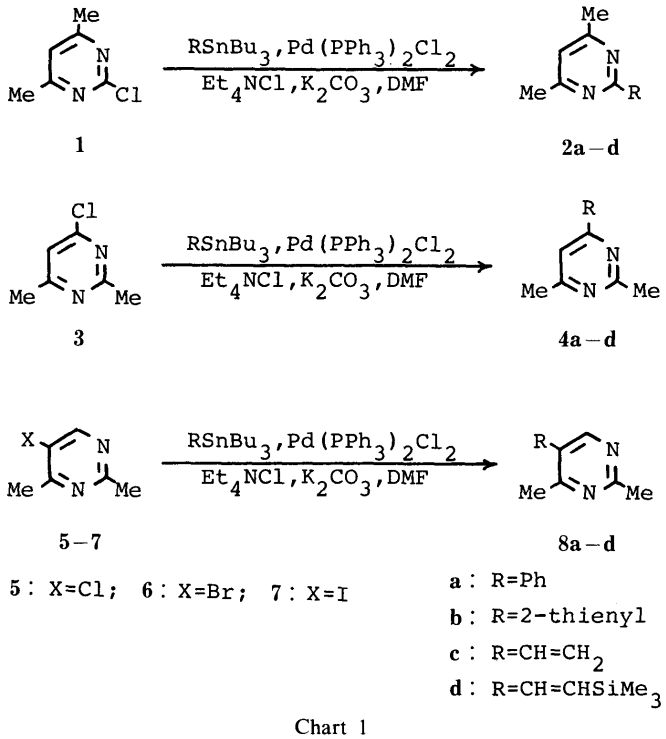

Chart 1

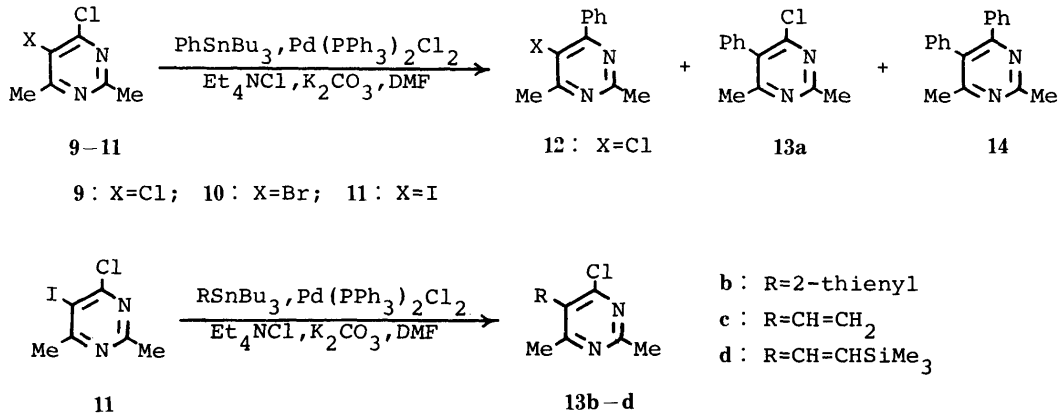

Chart 2

TABLE I. Palladium-Catalyzed Reaction of Halopyrimidines with Tributylstannanes

Starting material No.	Reaction time (h)	Product No.	Yield (%)	bp (°C)/mmHg	mp (°C)	Appearance[a]
1	3	**2a**	60	120—130/3	80—83[b]	Colorless needles
1	2	**2b**	88	120/3	83—85	Colorless prisms
1	2	**2c**	45	90—100/3		
1	2	**2d**	73	130—140/30		
3	3	**4a**	71	110—120/3[c]		
3	2	**4b**	88	120/3	68—70	Colorless prisms
3	2	**4c**	52	110—120/3		
3	2	**4d**	78	120—130/30		
5	8	**8a**	0			
6	8	**8a**	71	110—115/3		
7	4	**8a**	92			
7	2	**8b**	95	110/3	53—55	Colorless prisms
7	2	**8c**	67	90—100/30		
7	2	**8d**	73	130—140/30		
9	6	**12** (X=Cl)	50	145—150/2		
		13a	0			
		14	0			
10	4	**12** (X=Br)	0			
		13a	7		105—107	Colorless prisms
		14	50			
11	7	**12** (X=I)	0			
		13a	73		90—91	Colorless prisms
		14	20			
11	4	**13b**	60	140/5	49—52	Colorless needles
11	5	**13c**	45	110/3		
11	5	**13d**	69	110/3		

a) All solid products were recrystallized from hexane. *b*) Lit.[16] mp 82—84 °C. *c*) Lit.[16] bp 124 °C/4 mmHg.

TABLE II. Spectral and Analytical Data for Aryl- and Vinylpyrimidines

No.	Solvent	^{1}H-NMR δ (ppm)	Formula	Analysis (%) Calcd (Found) C	H	N
2b	CCl_4	2.42 (6H, s), 6.65 (1H, s), 7.01 (1H, dd, J=4.0 and 5.0), 7.31 (1H, dd, J=1.5 and 5.0), 7.89 (1H, dd, J=1.5 and 4.0)	$C_{10}H_{10}N_2$	63.13 (63.31)	5.30 (5.40)	14.72 (14.70)
2c	$CDCl_3$	2.47 (6H, s), 5.67 (1H, dd, J=4.0 and 9.0), 6.6—7.0 (3H, m)	$C_8H_{10}N_2$	71.61 (71.11)	7.51 (7.63)	20.87 (20.65)
2d	$CDCl_3$	0.18 (9H, s), 2.47 (6H, s), 6.84 (1H, s), 7.00 (1H, d, J=19.0), 7.44 (1H, d, J=19.0)	$C_{11}H_{18}N_2Si$	64.02 (64.08)	8.79 (8.59)	13.57 (13.38)
4b	CCl_4	2.44 (3H, s), 2.62 (3H, s), 7.10 (1H, s), 7.05 (1H, dd, J=4.0 and 5.0), 7.37 (1H, dd, J=1.5 and 5.0) 7.62 (1H, dd, J=1.5 and 4.0)	$C_{10}H_{10}N_2S$	63.13 (63.03)	5.30 (5.37)	14.72 (14.68)
4c	$CDCl_3$	2.48 (3H, s), 2.68 (3H, s), 5.62 (1H, dd, J=2.5 and 9.5), 6.2—6.8 (2H, m), 6.95 (1H, s)	$C_8H_{10}N_2$	71.61 (71.77)	7.51 (7.56)	20.87 (20.97)
4d	$CDCl_3$	0.18 (9H, s), 2.49 (3H, s), 2.70 (3H, s), 6.85 (1H, d, J=19.0), 7.02 (1H, s), 7.23 (1H, d, J=19.0)	$C_{11}H_{18}N_2Si$	64.02 (63.52)	8.79 (8.70)	13.57 (13.24)
8a	$CDCl_3$	2.48 (3H, s), 2.76 (3H, s), 7.2—7.6 (5H, m), 8.47 (1H, s)	$C_{12}H_{12}N_2$	78.23 (78.64)	6.57 (6.71)	15.20 (15.25)
8b	CCl_4	2.53 (3H, s), 2.96 (3H, s), 7.0—7.2 (2H, m), 7.3—7.4 (1H, m), 8.42 (1H, s)	$C_{10}H_{10}N_2S$	63.13 (63.21)	5.34 (5.34)	14.72 (14.80)
8c	$CDCl_3$	2.50 (3H, s), 2.68 (3H, s), 5.41 (1H, dd, J=1.5 and 11.0), 5.66 (1H, dd, J=1.5 and 18.5), 6.85 (1H, dd, J=11.0 and 18.5), 8.57 (1H, s)	$C_8H_{10}N_2$	71.61 (71.87)	7.51 (7.69)	20.87 (20.58)
8d	$CDCl_3$	0.17 (9H, s), 2.52 (3H, s), 2.67 (3H, s), 6.44 (1H, d, J=19.0), 6.92 (1H, d, J=19.0), 8.58 (1H, s)	$C_{11}H_{18}N_2Si$	64.02 (63.84)	8.79 (8.84)	13.57 (13.09)
12	$CDCl_3$	2.66 (3H, s), 2.73 (3H, s), 7.2—7.9 (5H, m)	$C_{12}H_{11}ClN_2$	65.91 (65.63)	5.07 (4.81)	12.81 (12.57)
13a	CCl_4	2.24 (3H, s), 2.63 (3H, s), 7.1—7.6 (5H, m)	$C_{12}H_{11}ClN_2$	65.91 (65.86)	5.07 (5.15)	12.81 (12.69)
14	CCl_4	2.31 (3H, s), 2.71 (3H, s), 7.0—7.5 (10H, m)	$C_{18}H_{16}N_2$	83.04 (83.05)	6.19 (6.30)	10.76 (10.69)
13b	CCl_4	2.35 (3H, s), 2.65 (3H, s), 6.9—7.3 (2H, m), 7.48 (1H, dd, J=2.0 and 7.0)	$C_{10}H_9ClN_2S$	53.45 (53.40)	4.04 (4.05)	15.78 (12.46)
13c	CCl_4	2.50 (3H, s), 2.58 (3H, s), 5.4—5.8 (3H, m), 6.5—7.0 (1H, m)	$C_8H_9ClN_2$[a]	168.0454 (168.0444)		
13d	CCl_4	0.18 (9H, s), 2.47 (3H, s), 2.56 (3H, s), 6.22 (1H, d, J=20.0), 6.80 (1H, d, J=20.0)	$C_{11}H_{15}ClN_2Si$	54.87 (54.60)	7.12 (7.08)	11.63 (11.67)

a) High-resolution MS value for the molecular ion is shown, because an analytically pure sample was not obtained.

2,4-dimethyl-5-phenylpyrimidine (**8a**), the relative reactivity of 5-bromo-2,4-dimethylpyrimidine (**6**) toward the cross-coupling reaction with tributylphenylstannane is between that of the 5-chloride (**5**) and the 5-iodide (**7**).

Based on the results described above, site-selectivity of the reaction was then investigated using 4,5-dihalo-2,6-dimethylpyrimidines (**9**—**11**) as substrates. When 4,5-dichloro-2,6-dimethylpyrimidine (**9**) was allowed to react with 1.5 eq of tributylphenylstannane under similar conditions, 5-chloro-2,4-dimethyl-6-phenylpyrimidine (**12**) was obtained as a sole product. In contrast, the reaction of 4-chloro-5-iodo-2,6-dimethylpyrimidine (**11**) with the phenylstannane gave 4-chloro-2,6-dimethyl-5-phenylpyrimidine (**13a**) as a major product accompanied with a small amount of 2,4-dimethyl-5,6-diphenylpyrimidine (**14**). In this case, no formation of 5-iodo-2,4-dimethyl-6-phenylpyrimidine was detected. Thus, it is reasonable that 5-(2-thienyl)- (**13b**), 5-vinyl- (**13c**), and 5-(2-trimethylsilyl)vinyl-4-chloro-2,6-dimethylpyrimidine (**13d**) were synthesized by the palladium-catalyzed cross-coupling reaction of **11** with the corresponding tributylstannane derivatives.

Finally, it should be mentioned that our present investigation may provide a general method for the synthesis of vinylpyrimidines. There are several papers dealing with the synthesis of vinylpyrimidines.[15-18] For example, the condensation of acetylacetone with 3-hydroxypropionamidine followed by thermal dehydration gave 4,6-dimethyl-2-vinylpyrimidine, but the yield of the product was not given in the report.[15] The chlorination of 2-(2-ethoxyethyl)-6-methyl-4(3*H*)-pyrimidinone with phosphoryl chloride is known to give 4-chloro-6-methyl-2-vinylpyrimidine in poor yield.[16] Furthermore, the synthesis of 4-vinylpyrimidines from 4-methylpyrimidine by the reaction with formaldehyde and the subsequent dehydration of pyrimidine-4-ethanol over solid potassium hydroxide gave 4-vinylpyrimidine in 23% yield.[17] Although the dehydrobromination of 5-(1-bromoethyl)pyrimidine with potassium *tert*-butoxide is known to give 5-vinylpyrimidine in 40% yield,[18] the synthesis of the bromoethylpyrimidine is inconvenient.

Compared with these reactions, our present method seems to have the advantages of experimental simplicity and general utility.

Experimental

Melting points and boiling points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, and m = multiplet. The mass spectrum (MS) was determined with a JEOL JMN-01SG-2 spectrometer.

General Procedure for the Cross-Coupling of Halopyrimidines with Aryl- and Vinyltributylstannanes A mixture of a halopyrimidine (1 mmol), an aryl- or a vinyltributylstannane (1.5 mmol), $Pd(PPh_3)_2Cl_2$ (16 mg), Et_4NCl (0.17 g, 1 mmol), K_2CO_3 (0.14 g, 1 mmol), and dimethylformamide (DMF) (2 ml) was heated under a nitrogen atmoshpere at 110 °C for an appropriate time (shown in Table I). The reaction mixture was diluted with water and extracted with ether. The crude product obtained from the ethereal extract was purified by silica gel column chromatography using $CHCl_3$ as an eluent, followed by recrystallization or distillation.

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