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Studies on Pyrimidine Derivatives. XXX.[1] The Palladium-Catalyzed Cross-Coupling Reaction of Iodopyrimidines with Terminal Olefinic Compounds[2]

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The influence of triphenylphosphine, used as a ligand, on the palladium-catalyzed cross-coupling reaction of iodopyrimidines with olefins such as ethyl acrylate, acrylonitrile, and styrene was investigated. In general, the addition of triphenylphosphine was concluded to retard the reaction in the pyrimidine series.

The effect of triphenylphosphine in the monoazine series is also discussed.

Keywords——palladium catalyst; carbon-carbon bond formation; homo-coupling reaction of *N*-heteroaromatic iodide; reaction conditions; six-membered *N*-heteroaromatic iodide; substituted ethenylpyrimidine

As reported previously,[3] we investigated the cross-coupling reaction of 2-, 4-, and 5-iodopyrimidines with terminal olefins such as ethyl acrylate, acrylonitrile, and styrene in the presence of palladium (II) acetate and triphenylphosphine, and found that 5-iodopyrimidines smoothly reacted with olefins to give 5-ethenylpyrimidines, as expected. In contrast, in the case of 4-iodopyrimidines, the homo-coupling reaction occurred in preference to the cross-coupling reaction with olefins under the same conditions, and the corresponding 4,4′-bipyrimidines were obtained. The reaction of 2-iodopyrimidines with olefins failed to give any significant products.

Since widely applicable methods for the preparation of pyrimidine derivatives having an olefinic side chain have not yet been established, we re-examined the reaction conditions, particularly the efficiency of various palladium catalysts and the influence of triphenylphosphine, and found the presence of triphenylphosphine to be rather unfavorable for the cross-coupling reaction at the 2- and 4-position of pyrimidine nuclei. The present paper deals with the reaction of iodopyrimidines, together with that of iodopyridines and iodoquinolines.

Reactions of 2-Iodo-4,6-dimethylpyridine

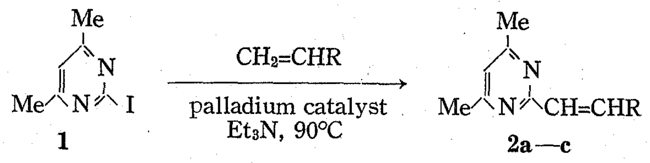
When palladium (II) acetate or chloride was used alone as a catalyst, 2-iodo-4,6-dimethylpyrimidine (**1**) reacted with ethyl acrylate in triethylamine at 90°C in a sealed tube to give ethyl 4,6-dimethyl-2-pyrimidineacrylate (**2a**) in 57% yield. Palladium (0) catalysts such as palladium black and palladium on charcoal (10%) were also effective for the cross-coupling reaction. However, the use of palladium (II) acetate and triphenylphosphine as a catalyst failed to yield any **2a**.

Similarly, in the reactions of **1** with acrylonitrile and styrene, the presence of triphenylphosphine was concluded to retard the reaction considerably. These results are listed in Table I.

Reactions of 4-Iodopyrimidines

In the reaction of 4-iodo-2,6-dimethylpyrimidine (**3a**) with ethyl acrylate, the use of palladium black or palladium on charcoal (10%) completely halted the formation of the homo-coupling product, 2,2′,6,6′-tetramethyl-4,4′-bipyrimidine (**5a**), and ethyl 2,6-dimethyl-4-pyrimidineacrylate (**4a**) was obtained as expected. However, these catalysts were not so effective in the cross-coupling reaction with olefins other than ethyl acrylate. For example, the reaction of **3a** with acrylonitrile or with styrene in the presence of palladium black gave a

Table I. Cross-coupling Reaction of 2-Iodo-4,6-dimethylpyrimidine (1) with Olefins

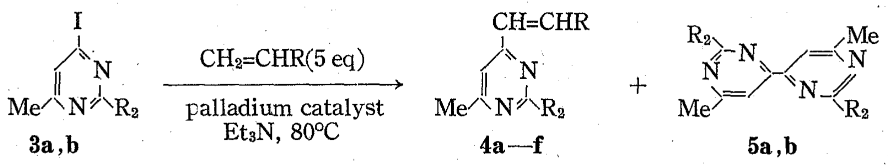


2a: R=COOEt
2b: R=CN
2c: R=Ph

Palladium catalyst	R	Reaction time (h)	Yield (%)	
			2	Recovery
$Pd(OAc)_2$–$2PPh_3$	COOEt	24	0	55
$Pd(OAc)_2$	COOEt	24	57	0
$PdCl_2$	COOEt	20	57	0
Pd black	COOEt	24	57	0
Pd carbon (10%)	COOEt	24	60	0
$Pd(OAc)_2$	CN	36	49a)	0
$PdCl_2$	CN	32	61b)	0
$Pd(OAc)_2$–$2PPh_3$	Ph	12	4	46
$Pd(OAc)_2$	Ph	12	52	0
$PdCl_2$	Ph	7	53	0
Pd black	Ph	12	31	21

a) *E*-isomer: *Z*-isomer=95: 5 by GC.
b) *E*-isomer, 24%; *Z*-isomer, 37% (isolated yield).

Table II. Cross-coupling Reaction of 4-Iodopyrimidines (3a, b) with Olefins



3a: R_2=Me
3b: R_2=^{i}Pr

4a: R_2=Me, R=COOEt
4b: R_2=Me, R=CN
4c: R_2=Me, R=Ph
4d: R_2=^{i}Pr, R=COOEt
4e: R_2=^{i}Pr, R=CN
4f: R_2=^{i}Pr, R=Ph

5a: R_2=Me
5b: R_2=^{i}Pr

Palladium catalyst	R_2	R	Reaction time (h)	Yield (%)		
				4	5	Recovery
$Pd(OAc)_2$–$2PPh_3$	Me	COOEt	68	6	0	58
$Pd(OAc)_2$	Me	COOEt	68	49	11	0
Pd black	Me	COOEt	68	77	0	0
Pd carbon (10%)	Me	COOEt	77	73	0	0
Pd black	Me	CN	50	37a)	58	0
Pd carbon (10%)	Me	CN	24	46	38	0
$Pd(OAc)_2$–$2PPh_3$	Me	Ph	36	0	0	60
$Pd(OAc)_2$	Me	Ph	36	55	17	0
Pd black	Me	Ph	36	47	19	0
Pd carbon (10%)	Me	Ph	22	50	23	0
$Pd(OAc)_2$–$2PPh_3$	^{i}Pr	COOEt	24	0	0	81
$Pd(OAc)_2$	^{i}Pr	COOEt	24	53	0	0
Pd black	^{i}Pr	COOEt	24	50	0	0
Pd carbon (10%)	^{i}Pr	COOEt	39	54	0	0
Pd carbon (10%)	^{i}Pr	CN	40	0	42	0
Pd carbon (10%)	^{i}Pr	Ph	48	57	0	0

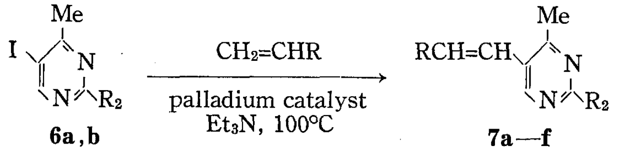
a) *E*-isomer: *Z*-isomer=68: 32 by GC.

considerable amount of **5a** together with 2,6-dimethyl-4-pyrimidineacrylonitrile (**4b**) or 2,6-dimethyl-4-styrylpyrimidine (**4c**) in 37 or 47% yields, respectively. Furthermore, the reaction of **3b** with acrylonitrile in the presence of palladium on charcoal resulted in the selective formation of 2,2′-diisopropyl-6,6′-dimethyl-4,4′-bipyrimidine (**5b**), whereas the reaction of **3b** with styrene over the same catalyst afforded 2-isopropyl-6-methyl-4-styrylpyrimidine (**4f**) as a sole product. Palladium (II) acetate and triphenylphosphine was almost wholly ineffective as a catalyst. The data listed in Table II indicate the need for further investigation on the catalysts.

Reactions of 5-Iodopyrimidines

As reported previously,[3] the palladium-catalyzed cross-coupling reaction of 5-iodo-2-isopropyl-4-methylpyrimidine (**6b**) with ethyl acrylate in the presence of the phosphine gave ethyl 2-isopropyl-4-methyl-5-pyrimidineacrylate (**7d**) in satisfactory yield. In this case, the reaction temperature should be over 130°C (in a sealed tube). However, when palladium (II) acetate was employed, the cross-coupling reaction proceeded at 100°C, giving **7d** in 85% yield. In contrast, palladium (II) acetate and triphenylphosphine gave only 7% yield of **7d**. These data together with those for 5-iodo-2,6-dimethylpyrimidine (**6a**) are summarized in Table III.

Table III. Cross-coupling Reaction of 5-Iodopyrimidines (**6a**, **b**) with Olefins



6a: R_2=Me **6b**: R_2=^{i}Pr

7a: R_2=Me, R=COOEt **7d**: R_2=^{i}Pr, R=COOEt
7b: R_2=Me, R=CN **7e**: R_2=^{i}Pr, R=CN
7c: R_2=Me, R=Ph **7f**: R_2=^{i}Pr, R=Ph

Palladium catalyst	R_2	R	Reaction time (h)	Yield (%) 7	Yield (%) Recovery
$Pd(OAc)_2$	Me	COOEt	24	71	0
Pd black	Me	COOEt	24	49	14
$Pd(OAc)_2$	Me	CN	24	68[a]	0
$Pd(OAc)_2$	Me	Ph	48	45	0
$Pd(OAc)_2$–$2PPh_3$	^{i}Pr	COOEt	4	7	77
$Pd(OAc)_2$	^{i}Pr	COOEt	4	85	0
Pd black	^{i}Pr	COOEt	4	87	0
$Pd(OAc)_2$	^{i}Pr	CN	12	72	0
$Pd(OAc)_2$	^{i}Pr	Ph[b]	24	79	0

a) *E*-isomer: *Z*-isomer=70: 30 by GC.
b) Reaction temperature: 120 °C.

In all the reactions of the above 2-, 4-, and 5-iodopyrimidines, the presence of triphenylphosphine appears to be unfavorable for the progress of the cross-coupling reaction.

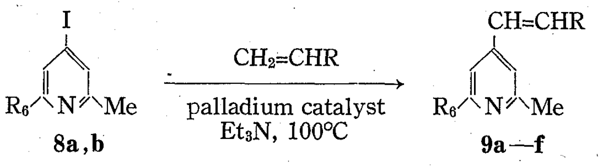
In order to confirm the generality of the above observations, the action of these palladium catalysts without triphenylphosphine was examined in the corresponding pyridine and quinoline series, but as described in the next section, the results suggested that the nature of the olefin cross-coupling reactions in heteroaromatics is rather complicated.

Unlike 4-iodopyrimidines (**3a**, **d**), 4-iodo-2-methyl- (**8a**) and 4-iodo-2,6-dimethyl-pyridine (**8b**) smoothly reacted with the olefins in the presence of palladium (II) acetate-triphenylphosphine to give the desired olefinic pyridines (**9a—f**), and 4,4′-bipyridines were not isolated. On the other hand, the reaction of 2-iodopyridine (**10**) with styrene gave mainly the homo-coupling product, 2,2′-bipyridine (**12**). In both cases the presence or absence of triphenylphosphine appeared to have no effect on the reaction. These results are summarized in Tables IV and V.

Reactions of Iodoquinolines

2-Iodo-4-methylquinoline (**13**) reacted with ethyl acrylate, acrylonitrile, and styrene in the presence of palladium (II) acetate alone to give the corresponding olefinic quinolines

TABLE IV. Cross-coupling Reaction of 4-Iodopyridines (**8a, b**) with Olefins

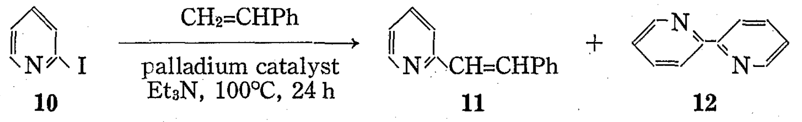


9a: $R_6=H$, $R=COOEt$
9b: $R_6=H$, $R=CN$
9c: $R_6=H$, $R=Ph$
9d: $R_6=Me$, $R=COOEt$
9e: $R_6=Me$, $R=CN$
9f: $R_6=Me$, $R=Ph$

8a: $R_6=H$
8b: $R_6=Me$

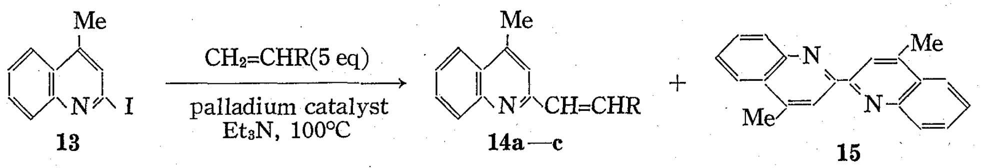
Palladium catalyst	R_6	R	Reaction time (h)	Yield (%)	
				9	Recovery
$Pd(OAc)_2$–$2PPh_3$	H	COOEt	24	64	0
$Pd(OAc)_2$–$2PPh_3$	H	CN	24	49	0
$Pd(OAc)_2$–$2PPh_3$	H	Ph	24	61	0
$Pd(OAc)_2$	H	Ph	24	55	0
$Pd(OAc)_2$–$2PPh_3$	Me	COOEt	24	49	0
$Pd(OAc)_2$–$2PPh_3$	Me	CN	24	69	0
$Pd(OAc)_2$–$2PPh_3$	Me	Ph	24	64	0

TABLE V. Cross-coupling Reaction of 2-iodopyridine (**10**) with Styrene



Palladium catalyst	Molar ratio of styrene	Yield (%)	
		11	**12**
$Pd(OAc)_2$–$2PPh_3$	1.2	11	66
$Pd(OAc)_2$–$2PPh_3$	5.0	7	71
$Pd(OAc)_2$	5.0	5	68

TABLE VI. Cross-coupling Reaction of 2-Iodo-methylquinoline (**13**) with Olefins



14a: R=COOEt
14b: R=CN
14c: R=Ph

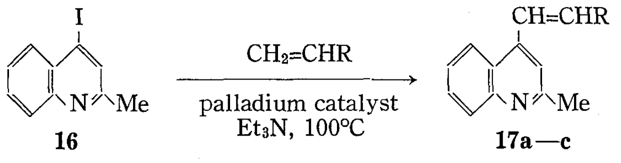
Palladium catalyst	R	Reaction time (h)	Yield (%)		
			14	**15**	Recovery
$Pd(OAc)_2$	COOEt	24	49	4	0
$Pd(OAc)_2$	CN	24	30[a]	3	0
$Pd(OAc)_2$–$2PPh_3$	Ph	24	15	5	35
$Pd(OAc)_2$	Ph	24	48	6	0

[a] In this case 4-methylquinoline-2-propionitrile was also obtained in 22% yield.

(**14a**—**c**) together with a small amount of 4,4′-dimethyl-2,2′-biquinoline (**15**). When triphenylphosphine was added to the reaction mixture, the yield of 4-methyl-2-styrylquinoline (**14c**) decreased and the recovery of **13** was substantial.

On the other hand, in the case of 4-iodo-2-methylquinoline (**16**), the presence of triphenylphosphine was necessary for the progress of of the reaction. Namely, when palladium (II) acetate was used alone, the yield of 2-methyl-4-styrylquinoline (**17c**) was only 5%, whereas the addition of triphenylphosphine improved the yield of **17c** to 46%. The data are listed in Tables VI and VII.

TABLE VII. Cross-coupling Reaction of 4-Iodo-2-methylquinoline (**16**) with Olefins



17a: R=COOEt
17b: R=CN
17c : R=Ph

Palladium catalyst	R	Reaction time (h)	Yield (%)	
			17	Recovery
$Pd(OAc)_2$–$2PPh_3$	COOEt	12	54	0
$Pd(OAc)_2$–$2PPh_3$	CN	6	57	0
$Pd(OAc)_2$–$2PPh_3$	Ph	24	31	54
$Pd(OAc)_2$–$2PPh_3$	Ph	48	46	21
$Pd(OAc)_2$	Ph	48	5	76

Heck *et al.*[4)] reported triphenylphosphine to be necessary in the palladium-catalyzed cross-coupling reaction of iodobenzenes. Our results obtained above are in contrast with their findings, although the role of the phosphine is not clear at present.

In conclusion, the palladium catalysts without the phosphine give good results in the pyrimidine series, but are not applicable in a straightforward way to the reactions of iodopyridines and quinolines.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer and a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Gas chromatograms were obtained on a Shimadzu GC-4CM gas chromatograph equipped with a hydrogen flame ionization detector.

Starting Iodoazines——The following iodoazines were prepared according to the literature: 2-iodo-4,6-dimethylpyrimidine (**1**),[5)] 4-iodo-2,6-dimethylpyrimidine (**3a**),[5)] 4-iodo-2-isopropyl-6-methylpyrimidine (**3b**),[6)] 5-iodo-2-isopropyl-4-methylpyrimidine (**6b**),[6)] 4-iodo-2-methylpyridine (**8a**),[7)] 4-iodo-2,6-dimethylpyridine (**8b**),[7)] 2-iodopyridine (**10**),[8)] 4-iodo-2-methylquinoline (**16**).[9)]

5-Iodo-2,4-dimethylpyrimidine (6a)——An EtOH (125 ml) solution of 4-chloro-5-iodo-2,6-dimethylpyrimidine[10)] (10.8 g, 40 mmol) and 90% $H_2NNH_2 \cdot H_2O$ (20 ml) was refluxed for 1 h. After removal of the EtOH under reduced pressure, the resulting solid was filtered off. A mixture of the solid and AgOAc (13.4 g, 80 mmol) in H_2O (40 ml) was refluxed for 2 h, then cooled, and the precipitate was filtered off. The filtrate was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The extract was dried over K_2CO_3 and the $CHCl_3$ was removed. Purification of the residue by Al_2O_3 column chromatography using hexane as an eluent gave colorless needles, mp 81—82°C, which were recrystallized from hexane. Yield 1.6 g (17%). ^{1}H-NMR ($CDCl_3$): 2.64 (6H, s), 8.82 (1H, s). *Anal.* Calcd for $C_6H_7IN_2$: C, 30.79; H, 3.02; N, 11.97. Found: C, 30.64; H, 3.03; N, 11.76.

2-Iodo-4-methylquinoline (13)——A mixture of 2-chloro-4-methylquinoine (10 g, 56 mmol), NaI(34 g, 220 mmol), and 56% HI (10 ml) in 2-butanone (240 ml) was refluxed with stirring for 24 h. After removal of the solvent under reduced pressure, the residue was made alkaline with K_2CO_3 and extracted with $CHCl_3$.

The $CHCl_3$ solution was washed with aq. Na_2SO_3 and dried over K_2CO_3. After removal of the $CHCl_3$, purification of the residue by Al_2O_3 column chromatography using C_6H_6 as an eluent gave pale yellow prisms, mp 87—89°C, which were recrystallized from ether–hexane. Yield 14 g (93%). ^{1}H-NMR ($CDCl_3$): 2.56 (3H, s), 7.47—8.06 (5H, m). *Anal.* Calcd for $C_{10}H_8IN$: C, 44.64; H, 3.00; N, 5.21. Found: C, 44.76; H, 3.04; N, 5.07.

General Procedure for Cross-coupling Reaction of Iodoazines with Olefins——A mixture of an iodoazine (5 mmol), an olefin (6 or 25 mmol; see Tables I—VII), a Pd catalyst (0.13 mmol), and Et_3N was heated in a sealed tube at an appropriate temperature for an appropriate time. The reaction mixture was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and the $CHCl_3$ was removed. The residue was purified by distillation under reduced pressure or by column chromatography.

Ethyl (*E*)-4,6-Dimethyl-2-pyrimidineacrylate (2a)——The crude product obtained by the reaction of 2-iodo-4,6-dimethylpyrimidine (1), ethyl acrylate (0.6 g, 6 mmol), $Pd(OAc)_2$, and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

4,6-Dimethyl-2-pyrimidineacrylonitrile (2b)——The crude product obtained by the reaction of **1**, acrylonitrile (0.3 g, 6 mmol), $PdCl_2$, and Et_3N (0.6 g, 6 mmol) was purified by silica gel column chromatography using C_6H_6: AcOEt (9: 1) as an eluant. The first eluate gave colorless needles (*E*-isomer) which were recrystallized from ether–hexane. The second eluate gave colorless scales (*Z*-isomer) which were recrystallized from ether–hexane.

The crude product was analyzed by gas chromatography (GC) [column, 3% OV-17 (2 m); column temperature, 200°C; flow rate of carrier gas (N_2), 60 ml/min].

4,6-Dimethyl-2(*E*)-styrylpyrimidine (2c)——i) The crude product obtained by the reaction of **1**, styrene (0.6 g, 6 mmol), $PdCl_2$, and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

ii) The crude product obtained by the reaction of **1**, styrene (0.6 g, 6 mmol), Pd black, and Et_3N (0.6 g, 6 mmol) was purified by silica gel column chromatography using C_6H_6 and C_6H_6: AcOEt (9: 1) as eluents. The C_6H_6 eluate gave the starting material (**1**) and the C_6H_6: AcOEt (9: 1) eluate gave **2c**.

Ethyl (*E*)-2,6-Dimethyl-4-pyrimidineacrylate (4a)——The crude product obtained by the reaction of 4-iodo-2,6-dimethylpyrimidine (**3a**), ethyl acrylate (2.5 g, 25 mmol), $Pd(OAc)_2$, and Et_3N (1.5 g, 15 mmol) was purified by silica gel column chromatography using C_6H_6, C_6H_6: AcOEt (9: 1), and AcOEt as eluents. The C_6H_6 eluate gave the starting material (**3a**). The C_6H_6: AcOEt (9: 1) eluate gave colorless needles (**4a**) which were recrystallized from hexane. The AcOEt eluate gave colorless needles (**5a**), mp 161—162°C (lit.[5] mp 157—158°C), which were recrystallized from acetone. ^{1}H-NMR ($CDCl_3$) (**5a**): 2.60 (6H, s), 2.78 (6H, s), 8.08 (2H, s).

2,6-Dimethyl-4-pyrimidineacrylonitrile (4b)——The crude product obtained by the reaction of **3a**, acrylonitrile (1.5 g, 25 mmol), 10% Pd-charcoal, and Et_3N (1.5 g, 15 mmol) was purified by silica gel column chromatography using C_6H_6: AcOEt (9: 1) and C_6H_6: AcOEt (8: 2) as eluents. The first eluate with C_6H_6: AcOEt (9: 1) and C_6H_6: AcOEt (8: 2) as eluents. The first eluate with C_6H_6: AcOEt (9: 1) gave colorless needles (*E*-isomer of **4b**) which were recrystallized from hexane. The second eluate gave a mixture of *E*- and *Z*-isomers of **4b**. The third eluate gave colorless needles (*Z*-isomer of **4b**) which were recrystallized from hexane. The C_6H_6: AcOEt (8: 2) eluate gave **5a**.

The crude product was analyzed by GC [column, 10% SE-30 (1 m); column temperature, 160°C; flow rate of carrier gas (N_2), 60 ml/min].

2,6-Dimethyl-4(*E*)-styrylpyrimidine (4c)——The crude product obtained by the reaction of **3a**, styrene (2.5 g, 25 mmol), $Pd(OAc)_2$, and Et_3N (1.5 g, 15 mmol) was purified by silica gel column chromatography using C_6H_6: AcOEt (9: 1) and AcOEt as eluents. The C_6H_6: AcOEt (9: 1) eluate gave colorless prisms (**4c**) which were recrystallized from ether–hexane and the AcOEt eluate gave **5a**.

Ethyl (*E*)-2-Isopropyl-6-methyl-4-pyrimidineacrylate (4d)——The crude product obtained by the reaction of 4-iodo-2-isopropyl-6-methylpyrimidine (**3b**), ethyl acrylate (2.5 g, 25 mmol), $Pd(OAc)_2$, and Et_3N (1.5 g, 15 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from petr. ether (bp 40—60°C) gave colorless needles.

Cross-coupling Reaction of 3b with Acrylonitrile——The crude product obtained by the reaction of **3b**, acrylonitrile (1.5 g, 25 mmol), 10% Pd-charcoal, and Et_3N (4 g, 40 mmol) was purified by silica gel column chromatography using AcOEt as an eluent. The AcOEt eluate gave colorless needles (**5b**), mp 139—140°C (lit.[3] mp 126—128°C), which were recrystallized from acetone.

2-Isopropyl-6-methyl-4(*E*)-styrylpyrimidine (4f)——The crude product obtained by the reaction of **3b**, styrene (2.5 g, 25 mmol), 10% Pd-charcoal, and Et_3N (1.5 g, 15 mmol) was distilled under reduced pressure to give a colorless liquid.

Ethyl (*E*)-2,4-Dimethyl-5-pyridimidineacrylate (7a)——The crude product obtained by the reaction of 5-iodo-2,4-dimethylpyrimidine (**6a**), ethyl acrylate (0.6 g, 6 mmol), Pd black, and Et_3N (0.6 g, 6 mmol) was sublimed at 120°C under reduced pressure (11 mmHg) to give the starting material (**6a**). The residue was distilled under reduced pressure to give a colorless solid. Recrystallization from ether–hexane gave colorless needles.

2,4-Dimethyl-5-pyrimidineacrylonitrile (7b)——The crude product obtained by the reaction of **6a**, acrylonitrile (0.3 g, 6 mmol), Pd(OAc)$_2$, and Et$_3$N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid (*E*- and *Z*-isomers of **7b**), bp 115—120°C (2 mmHg). Recrystallization from hexane gave colorless needles (*E*-isomer of **7b**).

The colorless solid was analyzed by GC [column, 3% OV-17 (2 m); column temperature, 190°C; flow rate of carrier gas (N$_2$), 60 ml/min]. ^{1}H-NMR (CDCl$_3$) (mixture of *E*- and *Z*-isomers): 2.53 (0.9H, s), 2.57 (2.1H, s), 5.65 (0.3H, d, $J=12$ Hz, olefinic proton of *Z*-isomer), 5.92 (0.7H, d, $J=16$ Hz, olefinic proton of *E*-isomer), 7.30 (0.3H, d, $J=12$ Hz, olefinic proton of *Z*-isomer), 7.50 (0.7H, d, $J=16$ Hz, olefinic proton of *E*-isomer), 8.61 (0.7H, s), 8.95 (0.3H, s).

2,4-Dimethyl-5(*E*)-styrylpyrimidine (7c)——The crude product obtained by the reaction of **6a**, styrene (0.6 g, 6 mmol), Pd(OAc)$_2$, and Et$_3$N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

Ethyl (*E*)-2-Isopropyl-4-methyl-5-pyrimidineacrylate (7d)——The crude product obtained by the reaction of 5-iodo-2-isopropyl-4-methylpyrimidine (**6b**), ethyl acrylate (0.6 g, 6 mmol), Pd(OAc)$_2$, and Et$_3$N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless liquid.

TABLE VIII. Physical Constants and Spectral Data for Olefinic Pyrimidines (**2**, **4**, and **7**)

				^{1}H-NMR (CDCl$_3$) δ	
Compd. No.	mp (°C)	bp (°C) [mmHg]	IR (CHCl$_3$) cm^{-1}	–CH=CH–[d] (*J*, Hz)	Other protons
2a(*E*)	54—56	132[2]	1720 1598	7.10 7.78 (16)	1.32 (3H, t, $J=7$ Hz), 2.48 (6H, s) 4.30 (2H,q, $J=7$ Hz), 6.97 (1H, s)
2b(*E*)	74—75	——	2230 1605	6.80 7.56 (16)	2.53 (6H, s), 7.08 (1H, s)
2b(*Z*)	82—83.5	——	2230 1605	5.87 7.29 (12)	2.58 (6H, s), 7.07 (1H, s)
2c(*E*)	47—48[a]	125[1]	1595	7.27 8.00 (16)	2.48 (6H, s), 6.85 (1H, s) 7.30—7.75 (5H, m)
4a(*E*)	67—69	114[1]	1715 1590	7.10 7.50 (16)	1.34 (3H, t, $J=7$ Hz), 2.50 (3H, s) 2.70 (3H, s), 4.29 (2H, q, $J=7$ Hz), 7.03 (1H, s)
4b(*E*)	70—72	101[1]	2225 1590	6.72 7.33 (16)	2.51 (3H, s), 2.69 (3H, s) 6.86 (1H, s)
4b(*Z*)	71—72	101[1]	2205 1585	5.83 7.06 (12)	2.56 (3H, s), 2.73 (3H, s) 7.36 (1H, s)
4c(*E*)	57—58[b]	——	1595	7.02 7.80 (16)	2.48 (3H, s), 2.71 (3H, s) 7.00 (1H, s), 7.30—7.67 (5H, m)
4d(*E*)	55—56	115—120[1]	1720 1590	7.02 7.62 (16)	1.33 (6H, d, $J=7$ Hz), 1.34 (3H, t, $J=7$ Hz), 2.52 (3H, s), 2.82—3.52 (1H, m) 4.52 (2H, q, $J=7$ Hz), 6.96 (1H, s)
4f(*E*)	——	140[1][c]	1590	6.93 7.93 (16)	1.34 (6H, d, $J=7$ Hz), 2.47 (3H, s) 2.85—3.54 (1H, m), 6.97 (1H, s) 7.30—7.63 (5H, m)
7a(*E*)	66[d]	115—120[2][e]	1715 1586	6.40 7.85 (16)	1.37 (3H, t, $J=7$ Hz), 2.63 (3H, s) 2.73 (3H, s), 4.32 (2H,q, $J=7$ Hz), 8.70 (1H, s)
7b(*E*)	91—92	——	2285 1585	5.83 7.54 (16)	2.56 (3H, s), 2.70 (3H,s) 8.58 (1H, s)
7c(*E*)	72—73[f]	120[2][g]	1582	——	2.63 (3H, s), 2.75 (3H, s),7.09 (2H, s) 7.20—7.76 (5H, m), 8.75 (1H, s)
7d(*E*)	——	135[2][h]	1720 1580	6.50 7.83 (18)	1.36 (6H, d, $J=7$ Hz), 1.38 (3H, t, $J=7$ Hz), 2.65 (3H, s), 2.90—3.60 (1H, m), 4.36 (2H, q, $J=7$ Hz), 8.90 (1H, s)
7e(*E*)	83—85[i]	125[1][j]	2200 1570	5.86 7.60 (16)	1.36 (6H, d, $J=7$ Hz), 2.60 (3H, s) 2.97—3.43 (1H, m), 8.65 (1H, s)
7f(*E*)	——	158[1][k]	1590	——	1.36 (6H, d, $J=7$ 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)

a) Lit.[11] mp 47—50°C. *b*) Lit.[12] mp 57—58°C. *c*) Lit.[11] bp 140—145°C (2 mmHg). *d*) Lit.[3] mp 68—69°C, bp 140—145°C (2 mmHg). *e*) Boiling point of an *E*- and *Z*-isomer mixture of **8b**. *f*) Lit.[3] mp 80—81°C. *g*) Lit.[3] bp 120°C (2 mmHg). *h*) Lit.[3] bp 135°C (2 mmHg). *i*) Lit.[3] mp 87—89°C. *j*) Lit.[3] bp 128—130°C (2 mmHg). *k*) Lit.[3] bp 180°C (2 mmHg).

(*E*)-2-Isopropyl-4-methyl-5-pyrimidineacrylonitrile (7e)——The crude product obtained by the reaction of **6b**, acrylonitrile (0.3 g, 6 mmol), $Pd(OAc)_2$, and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

2-Isopropyl-4-methyl-5(*E*)-styrylpyrimidine (7f)——The crude product obtained by the reaction of **6b**, styrene (0.6 g, 6 mmol), $Pd(OAc)_2$, and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless liquid.

TABLE IX. Analytical Data for Olefinic Pyrimidines (**2**, **4**, and **7**)

Compd. No.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
2a(*E*)	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58	64.09	6.89	14.09
2b(*E*)	$C_9H_9N_3$	67.90	5.70	26.40	68.03	5.67	26.44
2b(*Z*)	$C_9H_9N_3$	67.90	5.70	26.40	67.87	5.59	26.17
4a(*E*)	$C_{11}H_{14}N_2O_3$	64.06	6.84	13.58	64.32	6.96	13.37
4b(*E*)	$C_9H_9N_3$	67.90	5.70	26.40	67.61	5.80	26.61
4b(*Z*)	$C_9H_9N_3$	67.90	5.70	26.40	67.93	5.57	26.44
4d(*E*)	$C_{13}H_{18}N_2O_2$	66.64	7.74	11.96	66.44	7.86	12.07
7b(*E*)	$C_9H_9N_3$	67.90	5.70	26.40	67.99	5.68	26.68
7b(*E* and *Z*)	$C_9H_9N_3$	67.90	5.70	26.40	67.82	5.70	26.17

Ethyl (*E*)-2-Methyl-4-pyridineacrylate (9a)——The crude product obtained by the reaction of 4-iodo-2-methylpyridine (**8a**), ethyl acrylate (0.6 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless plates.

(*E*)-2-Methyl-4-pyridineacrylonitrile (9b)——The crude product obtained by the reaction of **8a**, acrylonitrile (0.3 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from ether–hexane gave colorless needles.

2-Methyl-4(*E*)-styrylpyridine (9c)——The crude product obtained by the reaction of **8a**, styrene (0.6 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was passed through a short column of Al_2O_3 using C_6H_6 as an eluent. The C_6H_6 eluate was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

Ethyl (*E*)-2,6-Dimethyl-4-pyridineacrylate (9d)——The crude product obtained by the reaction of 4-iodo-2,6-dimethylpyridine (**8b**), ethyl acrylate (0.6 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless plates.

(*E*)-2,6-Dimethyl-4-pyridineacrylonitrile (9e)——The crude product obtained by the reaction of **8b**, acrylonitrile (0.3 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

2,6-Dimethyl-4(*E*)-styrylpyridine (9f)——The crude product obtained by the reaction of **8b**, styrene (0.6 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless solid. Recrystallization from hexane gave colorless needles.

2(*E*)-Styrylpyridine (11)——The crude product obtained by the reaction of 2-iodopyridine (**10**), styrene (0.6 g, 6 mmol), $Pd(OAc)_2$, PPh_3 (60 mg, 0.26 mmol), and Et_3N (0.6 g, 6 mmol) was purified by silica gel column chromatography using C_6H_6: AcOEt (9: 1) as an eluent. The first eluate gave colorless needles (**11**) which were recrystallized from ether–hexane. The second eluate gave colorless prisms (**12**), mp 69.5—71.5°C (lit.[12]) mp 70.5—71.5°C), which were recrystallized from ether–hexane. ^{1}H-NMR ($CDCl_3$) (**12**): 7.25—7.46 (2H, m), 7.73—8.02 (2H, m), 8.43—8.82 (4H, m).

Ethyl (*E*)-4-Methyl-2-quinolineacrylate (14a)——The crude product obtained by the reaction of 2-iodo-4-methylquinoline (**13**), ethyl acrylate (2.5 g, 25 mmol), $Pd(OAc)_2$, and Et_3N (1.5 mmol) was extracted with acetone. The acetone-insoluble solid was recrystallized from $CHCl_3$–acetone to give colorless needles (**15**), mp 277—279°C (lit.[14]) mp 280—281°C). ^{1}H-NMR (CF_3COOH) (**15**): 3.30 (6H, s), 8.22—8.72 (10H, m). The residue obtained from the acetone extract was passed through a short column of Al_2O_3 using C_6H_6 as an eluent. The C_6H_6 eluate gave colorless needles (**14a**) which were recrystallized from ether–hexane.

Cross-coupling Reaction of 13 with Acrylonitrile——The crude product obtained by the reaction of **13**, acrylonitrile (1.5 g, 25 mmol), $Pd(OAc)_2$, and Et_3N (1.5 g, 15 mmol) was extracted with acetone. The acetone-insoluble solid was **15**. The residue obtained from the acetone extract was purified by silica gel column chromatography using C_6H_6 as an eluent. The first eluate gave colorless needles, (*E*)-4-methyl-2-

quinolineacrylonitrile (**14b**), which were recrystallized from ether–hexane. The second eluate gave 4-methylquinolinepropionitrile as pale yellow needles, mp 82—83°C, which were recrystallized from ether–hexane. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2240, 1605. ^{1}H-NMR (CDCl$_3$): 2.70 (3H, s), 2.80—3.40 (4H, m), 7.13 (1H, s), 7.33—8.10 (4H, m). *Anal.* Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.82; H, 6.16; N, 13.98.

4-Methyl-2(*E*)-styrylquinoline (14c)——The crude product obtained by the reaction of **13**, styrene (2.5 g, 25 mmol), Pd(OAc)$_2$, PPh$_3$ (60 mg, 0.26 mmol), and Et$_3$N (1.5 g, 15 mmol) was extracted with acetone. The acetone-insoluble solid was **15**. The residue obtained from the acetone extract was purified by silica gel column chromatography using C_6H_6 and C_6H_6: AcOEt (9: 1) as eluents. The C_6H_6 eluate gave the starting material (**13**). The C_6H_6: AcOEt (9: 1) eluate gave colorless needles (**14c**) which were recrystallized from ether.

Table X. Physical Constants and Spectral Data for Olefieic Pyridines (**9** and **11**) and Quinolines (**14** and **17**)

Compd. No.	mp (°C)	bp (°C) [mmHg]	IR (CHCl$_3$) cm^{-1}	^{1}H-NMR (CDCl$_3$) δ	
				–CH=CH–[d] (*J*, Hz)	Other protons
9a(*E*)	45—47	115—118[2]	1710 1615	6.60 7.61 (16)	1.33 (3H, t, *J*=7 Hz), 2.58 (3H, s) 4.30 (2H, q, *J*=7 Hz), 7.22 (1H, d, *J*=5 Hz) 7.25 (1H, s), 8.57 (1H, d, *J*=5 Hz)
9b(*E*)	85—86.5	123[3]	2210 1610	6.12 7.38 (17)	2.59 (3H, s), 7.20 (1H, d, *J*=6 Hz) 7.25 (1H, s), 8.63 (1H, d, *J*=6 Hz)
9c(*E*)	64—65	153—158[3]	1610	——	2.63 (3H, s), 7.02—7.70(9H, m) 8.62 (1H, d, *J*=5 Hz)
9d(*E*)	45—46	126[3]	1715 1620	6.57 7.57 (16)	1.30 (3H, t, *J*=7 Hz), 2.52 (6H, s) 4.28 (2H, q, *J*= 7 Hz, 7.04 (2H, s)
9e(*E*)	82—84	123[4]	2220 1620	6.08 7.33 (17)	2.56 (6H, s), 7.02 (2H, s)
9f(*E*)	56—57	142[3]	1608	——	250 (6H, s), 6.85—7.54 (9H, m)
11(*E*)	91.5—93[a]	——	1600	——	7.04—7.88 (10H,m), 8.68 (1H, d, *J*=5 Hz)
14a(*E*)	111—113	——	1710 1600	7.02 7.88 (16)	1.40 (3H, t, *J*=8 Hz), 2.76 (3H, s) 4.35 (2H, q, *J*=8 Hz), 7.32—8.22 (5H, m)
14b(*E*)	75—77	——	2235 1602	6.63 7.50 (16)	2.70 (3H, s), 7.23—8.16 (5H, m)
14c(*E*)	119—120.5	——	1608	——	2.66 (3H, s), 7.17—8.15 (12H, m)
17a(*E*)	——	168[1]	1718 1600	6.54 8.35 (16)	1.30 (3H, t, *J*=7 Hz), 2.73 (3H, s) 4.32 (2H, q, *J*=7Hz), 7.30—8.15 (5H, m)
17b(*E*)	119—121	——	2220 1595	6.06 —— (16)	2.76 (3H, s), 7.33—8.23 (6H, m)
17c(*E*)	99—101[b]	——	1602	——	2.72 (3H, s), 7.18—8.22 (12 m)

a) Lit.[15] mp 90.5—91°C. b) Lit.[16] mp 95—96°C.

Table XI. Analytical Data for Olefinic Pyridines (**9**) and Quinolines (**14** and **17**)

Compd. No.	Formula	Analysis (%)					
		Calcd			Found		
		C	H	N	C	H	N
9a(*E*)	$C_{11}H_{13}NO_2$	69.09	6.85	7.33	68.81	6.87	7.21
9b(*E*)	$C_9H_8N_2$	74.97	5.59	19.43	75.12	5.66	19.54
9c(*E*)	$C_{14}H_{13}N$	86.11	6.71	7.17	86.17	6.53	6.93
9d(*E*)	$C_{12}H_{15}NO_2$	70.22	7.37	6.82	69.87	7.39	6.63
9e(*E*)	$C_{10}H_{10}N_2$	75.92	6.37	17.71	76.16	6.47	17.65
9f(*E*)	$C_{15}H_{15}N$	86.08	7.22	6.69	86.19	7.03	6.51
14a(*E*)	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.58	6.30	5.82
14b(*E*)	$C_{13}H_{10}N_2$	80.38	5.19	14.42	80.47	5.24	14.28
14c(*E*)	$C_{18}H_{15}N$	88.13	6.16	5.71	88.39	6.13	5.42
17a(*E*)	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.33	6.42	5.78
17b(*E*)	$C_{13}H_{10}N_2$	80.38	5.19	14.42	80.39	4.98	14.15

Ethyl (*E*)-2-Methyl-4-quinolineacrylate (17a)——The crude product obtained by the reaction of 4-iodo-2-methylquinoline (**16**), ethyl acrylate (0.6 g, 6 mmol), Pd(OAc)$_2$, PPh$_3$ (60 mg, 0.26 mmol), and Et$_3$N (0.6 g, 6 mmol) was distilled under reduced pressure to give a colorless liquid.

(*E*)-2-Methyl-4-quinolineacrylonitrile (17b)——The crude product obtained by the reaction of **16**, acrylonitrile (0.3 g, 6 mmol), Pd(OAc)$_2$, PPh$_3$ (60 mg, 0.26 mmol), and Et$_3$N (0.6 g, 6 mmol) was passed through a short column of Al$_2$O$_3$ using hexane as an eluent. The hexane eluate gave colorless needles which were recrystallized from hexane.

2-Methyl-4(*E*)-styrylquinoline (17c)——The crude product obtained by the reaction of **16**, styrene (0.6 g, 6 mmol), Pd(OAc)$_2$, PPh$_3$ (60 mg, 0.26 mmol), and Et$_3$N (0.6 g, 6 mmol) was purified by silica gel column chromatography using C$_6$H$_6$: AcOEt (9: 1) as an eluent. The first eluate gave the starting material (**16**) and the second eluate gave colorless needles (**17c**) which were recrystallized from ether–hexane.

References and Notes

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