DIRECT INTRODUCTION OF ACYL AND ETHOXYCARBONYL GROUPS INTO PYRIMIDINE RING THROUGH THE TRIMETHYLSTANNYL DERIVATIVES

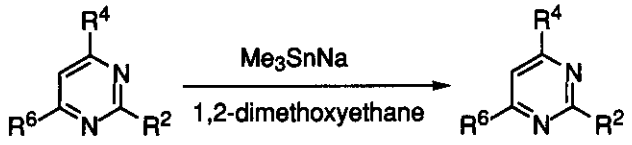
Yutaka Yamamoto*, Hidekazu Ouchi, Takuo Tanaka, and Yasuo Morita

Tohoku College of Pharmacy, 4-1, Komatsushima 4 chome, Aoba-ku, Sendai 981, Japan

Abstract – The reactions of acylformyl chlorides with 2- and 4-trimethylstannylpyrimidine derivatives proceeded more smoothly than those of acyl chlorides giving the corresponding 2- and 4-acylpyrimidines. Employing ethyl chloroglyoxylate instead of the acylating agent yielded the ethoxycarbonylpyrimidines. Similarly, the stepwise acylation and ethoxycarbonylation of bis(trimethylstannyl)pyrimidines provided pyrimidines having two different carbon functional groups.

Organostannyl groups have been playing an increasingly important role in synthetic chemistry,[1] especially in π-electron deficient *N*-heterocyclic compounds as a method for carbon-carbon bond formations.[2] Previous work[3] from this laboratory demonstrated that the replacement of trimethylstannyl (TMSn) groups at the α-position of the pyridine ring readily takes place by the reaction with acyl chlorides giving the corresponding α-acylated derivatives, whereas those of the TMSn groups at the other positions require a Pd catalyst. Recently,[4] the characteristic reactivity of the α-TMSn groups was extended to the effective acylation and ethoxycarbonylation using acylformyl chlorides and ethyl chloroglyoxylate, which react more smoothly with 2-(TMSn)pyridine, -quinoline, and 1-(TMSn)isoquinoline than acyl chlorides giving the corresponding acyl derivatives with loss of carbon monoxide. Undheim *et al.*[5] reported the synthesis of acetylpyrimidines from halopyrimidines. Namely, they obtained 2-, 4-, and 5-acetylpyrimidines through the cross-coupling reaction between the halopyrimidines and (1-ethoxyethenyl)tributylstannane, followed by acid hydrolysis of the thus formed α-ethoxyethenylpyrimidines. They also reported[6] the synthesis of 5-acylpyrimidines from 5-trialkylstannylpyrimidines and acyl chlorides in

the presence of a Pd catalyst. In the present paper, we describe the direct introduction of acyl and ethoxycarbonyl groups at the 2- and 4-positions of the pyrimidine ring through the mono- and bis(TMSn)pyrimidines. The starting mono- and bis(TMSn)pyrimidines (**2a-d**) were prepared from the corresponding chloro- and dichloropyrimidines (**1a-d**) and (TMSn)sodium according to a previously reported method[2] (Scheme 1). Benzoyl- (**3a**), cyclohexanecarbonyl- (**3b**), benzoylformyl- (**3c**), pyruvoyl chlorides (**3d**), and ethyl chloroglyoxylate (**3e**) were used as the acylating and ethoxycarbonylating agents.



1a: R^2 = Cl, R^4 = R^6 = Me
1b: R^2 = R^6 = Me, R^4 = Cl
1c: R^2 = R^4 = Cl, R^6 = Me
1d: R^2 = Me, R^4 = R^6 = Cl

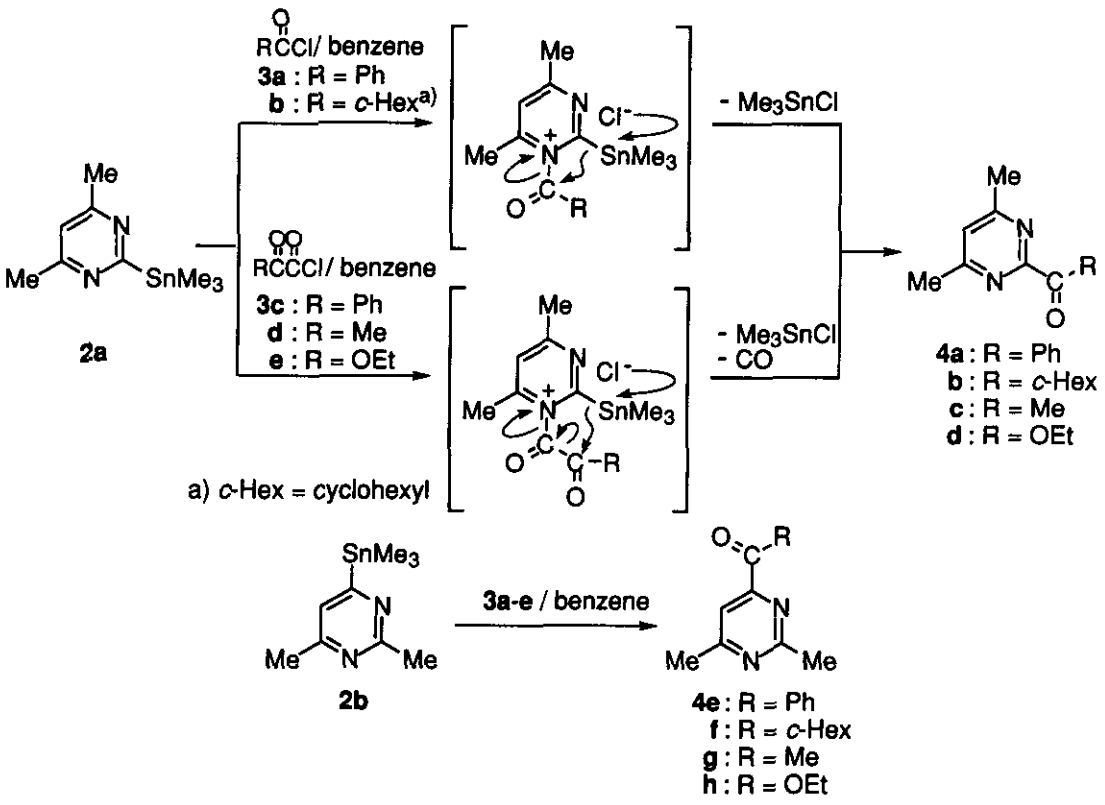
2a: R^2 = $SnMe_3$, R^4 = R^6 = Me
2b: R^2 = R^6 = Me, R^4 = $SnMe_3$
2c: R^2 = R^4 = $SnMe_3$, R^6 = Me
2d: R^2 = Me, R^4 = R^6 = $SnMe_3$

Scheme 1

First, the acylation of the 2- and 4-(TMSn)pyrimidines (**2a,b**) with **3a-e** was carried out. The treatment of 2-(TMSn)pyrimidine (**2a**) with **3a** and **3b** in benzene under reflux produced the corresponding 2-benzoyl (**4a**) and 2-cyclohexylcarbonyl derivatives (**4b**) in 52% and 89% yields, respectively (Table I, entries 2 and 4). When **3c-e** were employed, the reactions with **2a** took place at room temperature with the loss of carbon monoxide to afford the corresponding 2-acyl (**4a,c**) and 2-ethoxycarbonyl derivatives (**4d**) in 80–97% yields (Table I, entries 5-7). The acylformyl chlorides are more reactive than the corresponding acyl chlorides. This observation is similar to that for the reaction of 2-(TMSn)pyridine, -quinoline, and 1-(TMSn)isoquinoline with acylformyl chlorides.[4] Analogously, the reaction of **2b** with **3a-e** afforded the corresponding **4e-h** (Table I, entries 8-14).

A probable pathway for the acylation at the α-positions to nitrogen on the pyrimidine ring would involve the formation of the quaternary salt as an intermediate and subsequent migration of the acyl group to the α-carbon as illustrated in Scheme 2.

Next, the mono- and diacylation (or ethoxycarbonylation) of 2,4-bis(TMSn)pyrimidine (**2c**) and 4,6-bis(TMSn)-pyrimidine (**2d**) was examined. Selective monoacylation of **2c** took place at the 4-position of **2c**; the reactions of **2c** with 1 equivalent of **3c-e** at room temperature provided the 4-substituted 2-(TMSn)pyrimidines (**6a-c**) in 68–84% yields (Scheme 3, Table II, entries 1-3). The use of 2 equivalents of **3c-e** in these reactions brought about



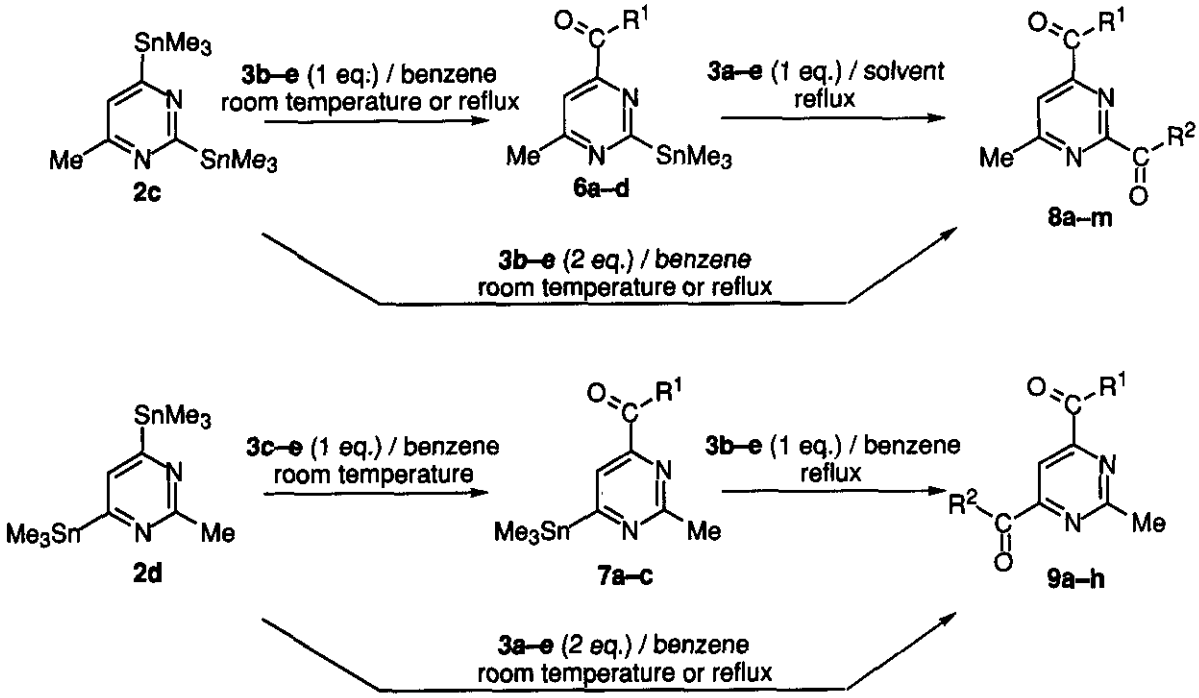
Scheme 2

Table I. Preparation of Acylpyrimidines (**4a-c,e-g**) and Ethoxycarbonylpyrimidines (**4d,h**)

Entry	Start. Comp.	Acylating Agent	Conditions Temp.	Time	Product	Yield (%)
1	**2a**	**3a**	room temperature	48 h	**4a**	21
2		**3a**	reflux	5 h	**4a**	52
3		**3b**	room temperature	60 h	**4b**	78
4		**3b**	reflux	5 h	**4b**	89
5		**3c**	room temperature	15 min	**4a**	97
6		**3d**	room temperature	10 min	**4c**	81
7		**3e**	room temperature	10 min	**4d**	80
8	**2b**	**3a**	room temperature	12 h	**4e**	39
9		**3a**	reflux	3 h	**4e**	46
10		**3b**	room temperature	24 h	**4f**	84
11		**3b**	reflux	3 h	**4f**	90
12		**3c**	room temperature	15 min	**4e**	98
13		**3d**	room temperature	15 min	**4g**	84
14		**4e**	room temperature	10 min	**4h**	76

diacylation (or diethoxycarbonylation) to produce the 2,4-diacyl (or diethoxycarbonyl) pyrimidines (**8a-c**) (Table II, entries 5-7). In contrast, the cyclohexylcarbonylation of **2c** (Table II, entries 4 and 8) required a higher reaction temperature (benzene refluxing for monoacylation and xylene refluxing for diacylation). In the case of **3a**, the reaction with **2c** gave only an unidentified tarry product. Both TMSn groups of 4,6-bis(TMSn)pyrimidine (**2d**) are enough reactive but the regioselective monoacylation (or ethoxycarbonylation) could be affected by controlling the amount of acylating (or ethoxycarbonylating) agents; treatment of **2d** with equimolar amounts of **3c-e** produced the 4-substituted 6-(TMSn)pyrimidines (**7a-c**) in 60–83% yields, while employing 2 equivalents of **3c-e** in the same reaction yielded the disubstituted derivatives (**9a-c**) (Scheme 3, Table II, entries 9-14).

Finally, the introduction of two different acyl groups into the pyrimidine ring by acylation (or ethoxycarbonylation) of the 4-substituted (TMSn)pyrimidines (**6a-d**, **7a-c**) with another mole of acylating (or ethoxycarbonylating) agents was achieved. For example, 4-benzoyl-2-(TMSn)pyrimidine (**6a**) was treated with **3d** and **3e** to give the corresponding 2,4-disubstituted pyrimidines (**8f,g**), respectively (Scheme 3, Table III, entries 4 and 5). The obtained results are summarized in Table III.



Scheme 3

Table II. Preparation of 4-Substituted Trimethylstannylpyrimidines (**6a-e**, **7a-c**), 2,4-Disubstituted (**8a-d**) and 4,6-Disubstituted Pyrimidines (**9a-c**)

Entry	Start. Comp.	Acylating Agent	Conditions Temp.	Time	Product	R^1	R^2	Yield (%)
1	**2c**	**3c**	room temperature	10 min	**6a**	Ph		79
2		**3d**	room temperature	10 min	**6b**	Me		84
3		**3e**	room temperature	10 min	**6c**	OEt		68
4		**3b**	reflux	5 h	**6d**	*c*-Hex		82
5		**3c**[a]	room temperature	15 min	**8a**	Ph	Ph	91
6		**3d**[a]	room temperature	30 min	**8b**	Me	Me	61
7		**3e**[a]	room temperature	3 h	**8c**	OEt	OEt	36
8		**3b**[a]	reflux[b]	5 h	**8d**	*c*-Hex	*c*-Hex	43
9	**2d**	**3c**	room temperature	10 min	**7a**	Ph		83
10		**3d**	room temperature	10 min	**7b**	Me		80
11		**3e**	room temperature	10 min	**7c**	OEt		60
12		**3c**[a]	room temperature	15 min	**9a**	Ph	Ph	97
13		**3d**[a]	room temperature	15 min	**9b**	Me	Me	63
14		**3e**[a]	room temperature	15 min	**9c**	OEt	OEt	49
15		**3a**[a]	reflux	10 h	**9a**	Ph	Ph	12
16		**3b**[a]	reflux	5 h	**9d**	*c*-Hex	*c*-Hex	41

a) Two equivalents of acylating agent were used. b) In xylene.

Table III. Preparation of 2,4-Disubstituted (**8a-m**) and 4,6-Disubstituted Pyrimidines (**9a-h**)

Entry	Start. Comp.	Acylating Agent	Conditions Solvent[a]	Time (h)	Product	R^1	R^2	Yield (%)
1	**6a**	**3a**	A	15	**8a**	Ph	Ph	10
2		**3b**	A	7	**8e**	Ph	*c*-Hex	11
3		**3c**	B	4	**8a**	Ph	Ph	86
4		**3d**	B	3	**8f**	Ph	Me	72
5		**3e**	B	4	**8g**	Ph	OEt	62
6	**6b**	**3c**	B	6	**8h**	Me	Ph	85
7		**3e**	B	5	**8i**	Me	OEt	33
8	**6c**	**3c**	B	5	**8j**	OEt	Ph	78
9		**3e**	B	5	**8c**	OEt	OEt	33
10	**6d**	**3a**	A	60	**8k**	*c*-Hex	Ph	17
11		**3b**	A	5	**8d**	*c*-Hex	*c*-Hex	46
12		**3c**	B	2	**8k**	*c*-Hex	Ph	91

Table III. (Continued)

Entry	Start. Comp.	Acylating Agent	Conditions Solvent[a)]	Time (h)	Product	R^1	R^2	Yield (%)
13		**3d**	B	4	**8l**	*c*-Hex	Me	75
14		**3e**	B	3	**8m**	*c*-Hex	OEt	43
15	**7a**	**3b**	B	96	**9e**	Ph	*c*-Hex	32
16		**3c**	B	4	**9a**	Ph	Ph	78
17		**3d**	B	2	**9f**	Ph	Me	70
18		**3e**	B	3	**9g**	Ph	OEt	60
19	**7b**	**3c**	B	2	**9f**	Me	Ph	78
20		**3e**	B	2	**9h**	Me	OEt	57
21	**7c**	**3c**	B	2	**9g**	OEt	Ph	67
22		**3d**	B	2	**9h**	OEt	Me	57

a) A: Xylene, B: Benzene

EXPERIMENTAL

Melting points are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. Mass spectra (ms) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. ^1H Nuclear magnetic resonance (nmr) spectra were recorded on a JEOL JNM-PMX 60 si spectrometer, using tetramethylsilane as an internal standard. Column chromatography was carried out on Merck Silica Gel 60 (230-400 mesh for flash chromatography).

4,6-Dimethyl-2-trimethylstannylpyrimidine (2a)

A solution of chlorotrimethylstannane (19.9 g, 100 mmol) in freshly distilled 1,2-dimethoxyethane (DME, 20 ml) was added dropwise to a stirred suspension of small cubes (*ca.* 2 mm cube) of Na metal (11.5 g, 0.5 g atom) in DME (50 ml) under N_2 stream in an ice-salt bath for 3 h (the color changes from white to green). The unreacted Na was removed by filtration through a fritted-glass filter funnel with large porosity under N_2 stream. A solution of 2-chloro-4,6-dimethylpyrimidine (**1a**, 11.4 g, 80 mmol) in DME (30 ml) was added dropwise to the above filtrate in an ice-salt bath. The reaction mixture was stirred for 2 h at the same temperature and then allowed to warm to room temperature. After removal of the solvent *in vacuo* at an ambient temperature, the residue was extracted with dry Et_2O. The Et_2O layer was dried, and concentrated under reduced pressure. The residue was purified by

distillation to give **2a** (13.9 g, 64 %) as a colorless liquid; bp 105–108 °C / 7 torr. Ir (neat) cm^{-1}: 772 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ: 0.36 (s, 9H), 2.43 (s, 6H), 6.83 (s, 1H). Ms (*m/z*): 272 (M^++1), 271 (M^+). *Anal.* Calcd for $C_9H_{16}N_2Sn$: C, 39.90; H, 5.95; N, 10,34. Found: C, 39.97; H, 6.14; N, 10.41.

2,4-Dimethyl-6-trimethylstannylpyrimidine (2b)

This compound was prepared from chlorotrimethylstannane (19.9 g, 100 mmol), Na metal (11.5 g, 0.5 g atom), and 4-chloro-2,6-dimethylpyrimidine (**1b**, 11.4 g, 80 mmol) according to the procedure described for the preparation of **2a**. Yield: 16.0 g (74 %); a colorless liquid; bp 101–103 °C / 4 torr. Ir (neat) cm^{-1}: 773 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.33 (s, 9H), 2.40 (s, 3H), 2.66 (s, 3H), 7.08 (s, 1H). Ms (*m/z*): 272 (M^++1), 271 (M^+). *Anal.* Calcd for $C_9H_{16}N_2Sn$: C, 39.90; H, 5.95; N, 10,34. Found: C, 39.74; H, 5.89; N, 10.10.

4-Methyl-2,6-bis(trimethylstannyl)pyrimidine (2c)

This compound was prepared from chlorotrimethylstannane (39.9 g, 200 mmol), Na metal (23.0 g, 1 g atom), and 2,4-dichloro-6-methylpyrimidine (**1c**, 13.0 g, 80 mmol) according to the procedure described for the preparation of **2a**. Yield: 20.2 g (60 %); a colorless liquid; bp 110–115 °C / 0.5 torr. Ir (neat) cm^{-1}: 770 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.36 (s, 18H), 2.40 (s, 3H), 7.37 (s, 1H). Ms (*m/z*): 422 (M^++2), 421 (M^++1), 420 (M^+). *Anal.* Calcd for $C_{11}H_{22}N_2Sn_2$: C, 31.48; H, 5.28; N, 6.67. Found: C, 31.60; H, 5.26; N, 6.56.

2-Methyl-4,6-bis(trimethylstannyl)pyrimidine (2d)

This compound was prepared from chlorotrimethylstannane (39.9 g, 200 mmol), Na metal (23.0 g, 1 g atom), and 4,6-dichloro-2-methylpyrimidine (**1d**, 13.0 g, 80 mmol) according to the procedure described for the preparation of **2a**. Yield: 21.1 g (63 %); a colorless liquid; bp 102–104 °C / 0.2 torr. Ir (neat) cm^{-1}: 771 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.35 (s, 18H), 2.70 (s, 3H), 7.32 (s, 1H). Ms (*m/z*): 422 (M^++2), 421 (M^++1), 420 (M^+). *Anal.* Calcd for $C_{11}H_{22}N_2Sn_2$: C, 31.48; H, 5.28; N, 6.67. Found: C, 31.22; H, 4.99; N, 6.39.

General Procedure for 2-Substituted 4,6-Dimethylpyrimidines (4a-d) and 4-Substituted 2,6-Dimethylpyrimidines (4e-h)

A solution of **3a-e** (6 mmol) in dry benzene (5 ml) was added dropwise to a stirred solution of **2a, b** (5 mmol) in dry benzene (10 ml) under N_2 stream. The mixture was stirred under the reaction conditions shown in Table I. The reaction mixture was washed with 10 % aqueous NH_3 solution (10 ml) and brine (10 ml), dried ($MgSO_4$),

and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

2-Benzoyl-4,6-dimethylpyrimidine (4a)

Flash column chromatography (Et_2O–hexane, 3 : 1) gave 1.03 g (97 %) of **4a** as colorless needles, mp 86–87 °C (petroleum ether). Ir (KBr) cm^{-1}: 1682 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.60 (s, 6H), 7.10-7.70 (m, 4H), 7.90-8.20 (m, 2H). Ms (*m/z*): 212 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.63; H, 5.63; N, 13.24.

2-Cyclohexylcarbonyl-4,6-dimethylpyrimidine (4b)

Flash column chromatography (Et_2O–hexane, 3 : 1) gave 0.97 g (89 %) of **4b** as colorless prisms, mp 44–44.5 °C (pentane). Ir (KBr) cm^{-1}: 1711 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.10-2.15 (m, 10H), 2.57 (s, 6H), 3.50-4.00 (m, 1H), 7.15 (s, 1H). Ms (*m/z*): 218 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.53; H, 8.48; N, 12.72.

2-Acetyl-4,6-dimethylpyrimidine (4c)

Flash column chromatography (Et_2O) gave 0.61 g (81 %) of **4c** as colorless prisms, mp 27 °C (pentane), bp 91–92 °C / 6 torr (lit.[8] bp 70–72 °C / 3 torr). Ir (KBr) cm^{-1}: 1713 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.60 (s, 6H), 2.77 (s, 3H), 7.20 (s, 1H). Ms (*m/z*): 150 (M^+).

2-Ethoxycarbonyl-4,6-dimethylpyrimidine (4d)

Flash column chromatography (AcOEt–hexane, 2 : 1) gave 0.72 g (80 %) of **4d** as a colorless liquid, bp 104–105 °C / 1 torr (lit.[9] bp 120–125 °C / 5 torr). Ir (neat) cm^{-1}: 1740 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.45 (t, J = 7 Hz, 3H), 2.60 (s, 6H), 4.53 (q, J = 7 Hz, 2H), 7.20 (s, 1H). Ms (*m/z*): 180 (M^+).

4-Benzoyl-2,6-dimethylpyrimidine (4e)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 1.04 g (98 %) of **4e** as colorless prisms, mp 69–70 °C (hexane). Ir (KBr) cm^{-1}: 1667 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.60 (s, 3H), 2.77 (s, 3H), 7.20-7.70, (m, 4H), 7.90-8.20 (m, 2H). Ms (*m/z*): 212 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.68; H, 5.71; N, 13.19.

4-Cyclohexylcarbonyl-2,6-dimethylpyrimidine (4f)

Flash column chromatography (Et_2O–hexane, 1 : 2) gave 0.98 g (90 %) of **4f** as a colorless liquid, bp 128 °C / 1 torr. Ir (neat) cm^{-1}: 1701 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.00-2.20 (m, 10H), 2.55 (s, 3H), 2.75, (s, 3H), 3.50-4.05 (m, 1H), 7.50 (s, 1H). Ms (*m/z*): 218 (M^+). *Anal.* Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.40; H, 8.31; N, 12.72.

4-Acetyl-2,6-dimethylpyrimidine (4g)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.63 g (84 %) of **4g** as colorless needles, mp 31–32 °C (pentane) (lit.[8] bp 96–98 °C / 20 torr). Ir (KBr) cm^{-1}: 1705
(C=O). ^1H Nmr ($CDCl_3$) δ : 2.60 (s, 3H), 2.70 (s, 3H), 2.80 (s, 3H), 7.56 (s, 1H). Ms (*m/z*): 150 (M^+).

4-Ethoxycarbonyl-2,6-dimethylpyrimidine (4h)

Flash column chromatography (Et_2O) gave 0.68 g (76 %) of **4h** as colorless needles, mp 34–35 °C (petroleum ether). Ir (KBr) cm^{-1}: 1719 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.43 (t, J = 7 Hz, 6H), 2.60 (s, 3H), 2.80 (s, 3H), 4.50 (q, J = 7 Hz, 2H), 7.78 (s, 1H). Ms (*m/z*): 180 (M^+). *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.12; H, 6.68; N, 15.35.

General Procedure for 4-Substituted 6-Methyl-2-trimethylstannylpyrimidines (6a-c)

A solution of **3c-e** (2.5 mmol) in dry benzene (5 ml) was added dropwise to a stirred solution of **2c** (1.05 g, 2.5 mmol) in dry benzene (10 ml) under N_2 stream for 10 min at room temperature. The reaction mixture was washed with saturated aqueous Na_2CO_3 solution (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel.

4-Benzoyl-6-methyl-2-trimethylstannylpyrimidine (6a)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.71 g (79 %) of **6a** as pale yellow prisms, mp 77–78 °C (pentane). Ir (KBr) cm^{-1}: 1664 (C=O), 768 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ: 0.40 (s, 9H), 2.63 (s, 3H), 7.30-7.80 (m, 4H), 8.10-8.40 (m, 2H). Ms (*m/z*): 362 (M^++1), 361 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2OSn$: C, 49.90; H, 5.03; N, 7.76. Found: C, 49.91; H, 4.94; N, 7.54.

4-Acetyl-6-methyl-2-trimethylstannylpyrimidine (6b)

Flash column chromatography (Et_2O–hexane, 1 : 5) gave 0.63 g (84 %) of **6b** as a colorless liquid, bp 112–114 °C / 2 torr. Ir (neat) cm^{-1}: 1708 (C=O), 775 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ: 0.43 (s, 9H), 2.60 (s, 3H), 2.73 (s, 3H), 7.58 (s, 1H). Ms (*m/z*): 300 (M^++1), 299 (M^+). *Anal.* Calcd for $C_{10}H_{16}N_2OSn$: C, 40.18; H, 5.39; N, 9.37. Found: C, 39.95; H, 5.18; N, 9.08.

4-Ethoxycarbonyl-6-methyl-2-trimethylstannylpyrimidine (6c)

Flash column chromatography (Et_2O–hexane, 1 : 10) gave 0.56 g (68 %) of **6c** as colorless prisms; mp 35–36 °C (pentane). Ir (KBr) cm^{-1}: 1746, 1720 (C=O), 778 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.42 (s, 9H), 1.43 (t, J = 7 Hz, 3H), 2.60 (s, 3H), 4.50 (q, J = 7 Hz, 2H), 7.68 (s, 1H). Ms (*m/z*): 330 (M^++1), 329 (M^+). *Anal.* Calcd for $C_{11}H_{18}N_2O_2Sn$: C, 40.16; H, 5.51; N, 8.52. Found: C, 40.06; H, 5.41; N, 8.32.

4-Cyclohexylcarbonyl-6-methyl-2-trimethylstannylpyrimidine (6d)

A stirred mixture of **2c** (1.05 g, 2.5 mmol) and **3b** (0.37 g, 2.5 mmol) in dry benzene (10 ml) was refluxed for 5 h under N_2 atmosphere. The reaction mixture was washed with saturated aqueous Na_2CO_3 solution (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using Et_2O–hexane (1 : 5) as an eluent to give **6d** (0.75 g, 82 %) as colorless prisms; mp 83–84 °C (pentane). Ir (KBr) cm^{-1}: 1695 (C=O), 771 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.40 (s, 9H), 1.10-2.15 (m, 10H), 2.55 (s, 3H), 3.53-4.05 (m, 1H), 7.50 (s, 1H). Ms (*m/z*): 368 (M^++1), 367 (M^+). *Anal.* Calcd for $C_{15}H_{24}N_2OSn$: C, 49.08; H, 6.59; N, 7.63. Found: C, 49.30; H, 6.70; N, 7.54.

General Procedure for 4-Substituted 2-Methyl-6-trimethylstannylpyrimidines (7a-c)

A solution of **3c-e** (2.5 mmol) in dry benzene (5 ml) was added dropwise to a stirred solution of **2d** (1.05 g, 2.5 mmol) in dry benzene (10 ml) under N_2 stream for 10 min at room temperature. The reaction mixture was washed with saturated aqueous Na_2CO_3 solution (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure.

4-Benzoyl-2-methyl-6-trimethylstannylpyrimidine (7a)

Yield 0.75 g (83 %); yellow needles; mp 55–57 °C (pentane), bp 143–145 °C / 0.1 torr. Ir (KBr) cm^{-1}: 1658 (C=O), 766 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.43 (s, 9H), 2.82 (s, 3H), 7.25-7.85 (m, 4H), 7.97-8.25 (m, 2H). Ms (*m/z*): 362 (M^++1), 361 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_2OSn$: C, 49.90; H, 5.03; N, 7.76. Found: C, 49.65;

H, 5.01; N, 7.54.

4-Acetyl-2-methyl-6-trimethylstannylpyrimidine (7b)

Yield 0.60 g (80 %); a colorless liquid; bp 104–106 °C / 1 torr. Ir (neat) cm^{-1}: 1707 (C=O), 775 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.38 (s, 9H), 2.68 (s, 3H), 2.80 (s, 3H), 7.81 (s, 1H). Ms (*m/z*): 300 (M^++1), 299 (M^+). *Anal.* Calcd for $C_{10}H_{16}N_2OSn$: C, 40.18; H, 5.39; N, 9.37. Found: C, 39.92; H, 5.11; N, 9.25.

4-Ethoxycarbonyl-2-methyl-6-trimethylstannylpyrimidine (7c)

Yield 0.50 g (60 %); a colorless liquid; bp 116–118 °C / 0.5 torr. Ir (neat) cm^{-1}: 1749, 1725 (C=O), 776 (–$SnMe_3$). ^1H Nmr ($CDCl_3$) δ : 0.43 (s, 9H), 1.43 (t, J = 7 Hz, 3H), 2.85 (s, 3H), 4.50 (q, J = 7 Hz, 2H), 7.90 (s, 1H). Ms (*m/z*): 330 (M^++1), 329 (M^+). *Anal.* Calcd for $C_{11}H_{18}N_2O_2Sn$: C, 40.16; H, 5.51; N, 8.52. Found: C, 39.88; H, 5.34; N, 8.23.

General Procedure for 2,4-Disubstituted 6-Methylpyrimidines (8a-d) and 4,6-Disubstituted 2-Methylpyrimidines (9a-d)

A solution of **3b-e** (6 mmol) in dry benzene (5 ml) was added dropwise to a stirred solution of **2c, d** (1.05 g, 2.5 mmol) in dry benzene (10 ml) under N_2 stream. The mixture was stirred under the reaction conditions shown in Table II. The reaction mixture was washed with 10 % aqueous NH_3 solution (10 ml) and brine (10 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

2,4-Dibenzoyl-6-methylpyrimidine (8a)

Flash column chromatography (Et_2O–hexane, 2 : 3) gave 0.69 g (91 %) of **8a** as colorless plates; mp 65–66 °C (hexane). Ir (KBr) cm^{-1}: 1676, 1664 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.70 (s, 3H), 7.10-8.30 (m, 11H). Ms (*m/z*): 302 (M^+). *Anal.* Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.58; H, 4.58; N, 9.16.

2,4-Diacetyl-6-methylpyrimidine (8b)

Flash column chromatography (Et_2O–hexane, 5 : 1) gave 0.27 g (61 %) of **8b** as colorless needles; mp 67–68 °C (pentane). Ir (KBr) cm^{-1}: 1707 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.77 (s, 3H), 2.80 (s, 3H), 2.85 (s, 3H), 7.90 (s,

1H). Ms (*m/z*): 178 (M^+). *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.61; H, 5.49; N, 15.52.

2,4-Diethoxycarbonyl-6-methylpyrimidine (8c)

Flash column chromatography (Et_2O) gave 0.24 g (36 %) of **8c** as colorless needles, mp 39–39.5 °C (pentane). Ir (KBr) cm^{-1}: 1746, 1715 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.47 (t, *J* =7Hz, 6H), 2.80 (s, 3H), 4.50 (q, *J* = 7 Hz, 2H), 4.53 (q, *J* = 7 Hz, 2H), 8.00 (s, 1H). Ms (*m/z*): 238 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.40; H, 5.90; N, 11.64.

2,4-Dicyclohexylcarbonyl-6-methylpyrimidine (8d)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.34 g (43 %) of **8d** as colorless prisms; mp 78 °C (pentane). Ir (KBr) cm^{-1}: 1704 (C=O). ^1H Nmr ($CDCl_3$) δ : 0.80-2.33 (m, 20H), 2.73 (s, 3H), 3.35-4.10 (m, 2H), 7.82 (s, 1H). *Ms* (*m/z*): 314 (M^+). *Anal.* Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.31; H, 8.45; N, 8.66.

4,6-Dibenzoyl-2-methylpyrimidine (9a)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.73 g (97 %) of **9a** as colorless needles; mp 116–117 °C (hexane). Ir (KBr) cm^{-1}: 1670, 1656 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.90 (s, 3H), 7.30-7.90 (m, 6H), 8.00-8.30 (m, 5H). Ms (*m/z*): 302 (M^+). *Anal.* Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.62; H, 4.55; N, 9.14.

4,6-Diacetyl-2-methylpyrimidine (9b)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.28 g (63 %) of **9b** as colorless needles, mp 40–41 °C (petroleum ether). Ir (KBr) cm^{-1}: 1714 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.76 (s, 6H), 2.95 (s, 3H), 8.16 (s, 1H). Ms (*m/z*): 178 (M^+). *Anal.* Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.79; H, 5.59; N, 15.57.

4,6-Diethoxycarbonyl-2-methylpyrimidine (9c)

Flash column chromatography (Et_2O–*hexane*, 3 : 1) gave 0.29 g (49 %) of **9c** as colorless needles; mp 61–62 °C (petroleum ether). Ir (KBr) cm^{-1}: 1728 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.50 (t, *J* =7Hz, 6H), 2.00 (s, 3H), 4.56 (q,

J = 7 Hz, 4H), 8.40 (s, 1H). Ms (*m/z*): 238 (M^+). *Anal.* Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.71; H, 5.96; N, 11.67.

4,6-Dicyclohexylcarbonyl-2-methylpyrimidine (9d)

Flash column chromatography (Et_2O–hexane, 1 : 10 ~ 1 : 1) gave 0.32 g (41 %) of **9d** as colorless needles; mp 55–56 °C (pentane). Ir (KBr) cm^{-1}: 1706 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.00-2.20 (m, 20H), 2.87 (s, 3H), 3.46-4.10 (m, 2H), 8.16 (s, 1H). Ms (*m/z*): 314 (M^+). *Anal.* Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.56; H, 8.45; N, 8.81.

General Procedure for Acylation (or Ethoxycarbonylation) of 4-Substituted 6-Methyl-2-trimethylstannylpyrimidines (6a-d) and 4-Substituted 2-Methyl-6-trimethylstannylpyrimidines (7a-c)

A solution of **3a-e** (0.6 mmol) in dry benzene (3 ml) was added dropwise to a stirred solution of **6a-d**, **7a-c** (0.5 mmol) in dry benzene (or xylene) (7 ml) under N_2 stream. The mixture was refluxed with stirring for the reaction conditions shown in Table III. The reaction mixture was washed with 10 % aqueous NH_3 solution (10 ml) and brine (10 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

2-Benzoyl-4-cyclohexylcarbonyl-6-methylpyrimidine (8e)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.02 g (11 %) of **8e** as colorless prisms; mp 80–81°C (pentane). Ir (KBr) cm^{-1}: 1712, 1660 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.03-2.23 (m, 10H), 2.77 (s, 3H), 3.40-3.93 (m, 1H), 7.25-7.76 (m, 3H), 7.89 (s, 1H), 8.10-8.36 (m, 2H). Ms (*m/z*): 308 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.21; H, 6.72; N, 8.86.

2-Acetyl-4-benzoyl-6-methylpyrimidine (8f)

Flash column chromatography (Et_2O–hexane, 3 : 1) gave 0.09 g (72 %) of **8f** as a colorless powder; mp 79–80 °C (hexane). Ir (KBr) cm^{-1}: 1712, 1674 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.77 (s, 6H), 7.30-7.76 (m, 3H), 7.90 (s, 1H), 8.06-8.32 (m, 2H). Ms (*m/z*): 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.80; H, 4.92; N, 11.47.

4-Benzoyl-2-ethoxycarbonyl-6-methylpyrimidine (8g)

Flash column chromatography (Et_2O–hexane, 4 : 1) gave 0.08 g (62 %) of **8g** as a colorless powder; mp 79–80 °C (hexane). Ir (KBr) cm^{-1}: 1749, 1664 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.43 (t, J = 7 Hz, 3H), 2.76 (s, 3H), 4.53 (q, J = 7 Hz, 2H), 7.26-7.76 (m, 3H), 7.86 (s, 1H), 8.05-8.37 (m, 2H). Ms (*m/z*): 270 (M^+). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.60; H, 5.05; N, 10.22.

4-Acetyl-2-benzoyl-6-methylpyrimidine (8h)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.10 g (85 %) of **8h** as a colorless powder, mp 86–87 °C (hexane). Ir (KBr) cm^{-1}: 1705, 1679 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.70 (s, 3H), 2.73 (s, 3H), 7.25-8.23 (m, 6H). Ms (*m/z*): 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.26; H, 5.16; N, 11.39.

4-Acetyl-2-ethoxycarbonyl-6-methylpyrimidine (8i)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.03 g (33 %) of **8i** as colorless needles; mp 92–93 °C (pentane). Ir (KBr) cm^{-1}: 1750, 1738, 1710 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.48 (t, J = 7 Hz, 3H), 2.76 (s, 3H), 2.80 (s, 3H), 4.57 (q, J = 7 Hz, 2H), 7.87 (s, 1H). Ms (*m/z*): 208 (M^+). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.77; H, 5.87; N, 13.30.

2-Benzoyl-4-ethoxycarbonyl-6-methylpyrimidine (8j)

Flash column chromatography (Et_2O–hexane–CH_2Cl_2, 1 : 3 : 1) gave 0.11 g (78 %) of **8j** as a colorless powder; mp 40 °C (hexane). Ir (KBr) cm^{-1}: 1733, 1688 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.43 (t, J = 7 Hz, 3H), 2.75 (s, 3H), 4.50 (q, J = 7 Hz, 2H), 7.30-7.75 (m, 3H), 7.93-8.30 (m, 3H). Ms (*m/z*): 270 (M^+). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.75; H, 5.17; N, 10.24.

2-Benzoyl-4-cyclohexylcarbonyl-6-methylpyrimidine (8k)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.14 g (91 %) of **8k** as colorless needles; mp 83–84 °C (pentane). Ir (KBr) cm^{-1}: 1695, 1686 (C=O). ^1H Nmr ($CDCl_3$) δ : 0.70-2.20 (m, 10H), 2.73 (s, 3H), 3.35-4.00 (m, 1H), 7.20-8.30 (m, 6H). Ms (*m/z*): 308 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.87; H, 6.49; N, 8.89.

2-Acetyl-4-cyclohexylcarbonyl-6-methylpyrimidine (8l)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.09 g (75 %) of **8l** as pale yellow prisms; mp 81–83 °C (pentane). Ir (KBr) cm^{-1}: 1709, 1699 (C=O). ^1H Nmr ($CDCl_3$) δ : 0.80-2.20 (m, 10H), 2.73 (s, 3H), 2.83 (s, 3H), 3.50-4.15 (m, 1H), 7.83 (s, 1H). Ms (*m/z*): 246 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.35; H, 7.51; N, 11.20.

4-Cyclohexylcarbonyl-2-ethoxycarbonyl-6-methylpyrimidine (8m)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.06 g (43 %) of **8m** as colorless needles; mp 137–138 °C (hexane). Ir (KBr) cm^{-1}: 1732, 1700 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.05-2.10 (m, 13H), 2.73 (s, 3H), 3.53-4.10 (m, 1H), 4.57 (q, J = 7 Hz, 2H), 7.83 (s, 1H). Ms (*m/z*): 276 (M^+). *Anal.* Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.36; H, 7.46; N, 10.05.

4--Benzoyl-6-cyclohexylcarbonyl-2-methylpyrimidine (9e)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.05 g (32 %) of **9e** as pale yellow prisms; mp 73 °C (hexane). Ir (KBr) cm^{-1}: 1698, 1668 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.05-2.20 (m, 10H), 2.90 (s, 3H), 3.50-4.10 (m, 1H), 7.25-7.75 (m, 3H), 7.97-8.23 (m, 3H). Ms (*m/z*): 308 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.12; H, 6.79; N, 9.03.

4-Acetyl-6-benzoyl-2-methylpyrimidine (9f)

Flash column chromatography (Et_2O–hexane, 1 : 3) gave 0.09 g (78 %) of **9f** as pale yellow prisms; mp 70–71 °C (hexane). Ir (KBr) cm^{-1}: 1706, 1672 (C=O). ^1H Nmr ($CDCl_3$) δ : 2.76 (s, 3H), 2.93 (s, 3H), 7.30-7.78 (m, 3H), 8.00-8.27 (m, 3H). Ms (*m/z*): 240 (M^+). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.75; H, 4.91; N, 11.50.

4-Benzoyl-6-ethoxycarbonyl-2-methylpyrimidine (9g)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.09 g (67 %) of **9g** as a colorless liquid; bp 165–168 °C / 0.4 torr. Ir (neat) cm^{-1}: 1748, 1728, 1674 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.45 (t, J = 7 Hz, 3H), 2.93 (s, 3H), 4.52 (q, J = 7 Hz, 2H), 7.25-7.73 (m, 3H), 7.97-8.20 (m, 2H), 8.26 (s, 1H). Ms (*m/z*): 270 (M^+). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.40; H, 5.47; N, 10.48.

4-Acetyl-6-ethoxycarbonyl-2-methylpyrimidine (9h)

Flash column chromatography (Et_2O–hexane, 1 : 1) gave 0.06 g (57 %) of **9h** as colorless needles; mp 75–76°C (pentane). Ir (KBr) cm^{-1}: 1746, 1709 (C=O). ^1H Nmr ($CDCl_3$) δ : 1.46 (t, J = 7 Hz, 3H), 2.73 (s, 3H), 2.92 (s, 3H), 4.52 (q, J = 7 Hz, 2H), 8.30 (s, 1H). Ms (*m/z*): 208 (M^+). *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.67; H, 5.84; N, 13.55.

ACKNOWLEDGEMENT

The authors wish to thank Mr. S. Satoh of this College for the measurements of mass spectra and microanalyses.

REFERENCES AND NOTES

1. M. Pereyre, J. -P. Quintard, and A. Rahm, " Tin in Organic Synthesis," Butterworths, London, 1987; J. L. Wardell, " The Use of Organotin Compounds in Organic Synthesis " in " Chemistry of Tin, " ed. by P. G. Harrison, Chapman and Hall, New York, 1989, pp. 315-358.
2. V. N. Kalinin, *Synthesis*, **1992**, 413.
3. Y. Yamamoto and A. Yanagi, *Chem. Pharm. Bull.*, 1982, **30**, 2003.
4. Details of the reaction of acylformyl chlorides with several α-(TMSn)azines will be reported in the near future.
5. M. J. Majeed, Ø. Antonsen, T. Benneche, and K. Undheim, *Tetrahedron*, 1989, **45**, 993; J. Solberg and K. Undheim, *Acta Chem. Scand., Ser. B*, 1989, **43**, 62.
6. K. Arukwe, T. Benneche, and K. Undheim, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 255.
7. Y. Yamamoto and A. Yanagi, *Chem. Pharm. Bull.*, 1982, **30**, 1731.
8. T. Sakamoto, T. Ono, T. Sakasai, and H. Yamanaka, *Chem. Pharm. Bull.*, 1980, **28**, 202.
9. T. Sakamoto, T. Ono, T. Sakasai, and H. Yamanaka, Abstracts of Papers, 12 th Congress of Heterocyclic Chemistry, Tokyo, Japan, 1979, p. 185.

Received, 1st February, 1995