Synthesis of 5-Substituted Pyrimidines. *ortho*-Directed Lithiation of Pyrimidine Derivatives [1]

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ortho-Directed lithiation of some pyrimidines has been investigated. Treatment of 2- and/or 4-alkoxy or acylaminopyrimidine with lithium 2,2,6,6-tetramethylpiperidide in ether at 0°, followed by quenching with various electrophiles afforded the corresponding 5-substituted pyrimidines.

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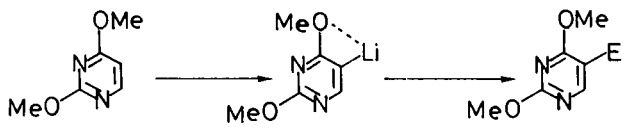
It is well known that *ortho*-directed lithiation of aromatics has been a powerful synthetic tool in organic chemistry due to its high regioselectivity [2]. However it suffers certain limitations in heteroaromatics except for pyridine ring [3]. Particularly, in the pyrimidine system, the lithiation has been carried out by halogen-lithium exchange [4] and there are few reports dealing with *ortho*-directed lithiation of pyrimidine having an *ortho*-activating group [5,6]. This paper describes the synthesis of 5-substituted pyrimidines through *ortho*-directed lithiation reactions including a full account of the work mentioned in the previous communication [1].

Treatment of an ether solution of 2,4-dimethoxypyrimidine (**1**) [7] in anhydrous ether with 1.2 equivalents of lithium diisopropylamide (LDA) at 0° for 5 minutes gave the *ortho*-lithio derivative **2**, which was quenched with benzaldehyde to afford the 5-substituted product **3a** in 5% yield with the recovery of the starting material (60%) (Scheme 1). Although the structure of **3a** was speculated on the basis of spectral data, mainly from an assignment of the nuclear magnetic resonance (^{1}H-nmr) spectra, final establishment was carried out by the identification with an authentic sample, which was prepared by the halogen-lithium exchange of 5-bromo-2,4-dimethoxypyrimidine [8], followed by treatment with benzaldehyde. In order to elucidate the most effective conditions for the *ortho*-lithiated intermediate, we examined under various conditions changing the reaction temperature, solvent, and the lithiating reagent. These results were summarized in Table 1, and the best result was obtained using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) [9] in ether at 0° (run 6).

Scheme 1



1 2

3a E=CH(OH)Ph
3b E=CH(OH)Me
3c E=CO_2Me
3d E=CHO
3e E=CO_2Et
3f E=$SiMe_3$
3g E=COMe

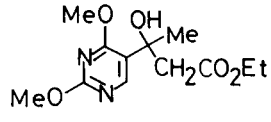


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Table 1

Yield of **3a** Under Various Reaction Conditions

Runs	Solvent	Base	Reaction Temperature (°C)	Yield (%) [a]
1	Et_2O	LDA [b]	-70	-[c]
2	Et_2O	LDA	-20	-
3	Et_2O	LDA	0	5
4	Et_2O	LDA	rt	16
5	Et_2O	LDA	40	24
6	Et_2O	LiTMP [d]	0	65
7	Et_2O	LiTMP	rt	52
8	Et_2O	LiTMP	40	24
9	THF	LDA	rt	20
10	THF	LiTMP	rt	24

[a] Isolated yield. [b] Lithium diisopropylamide. [c] Trace. [d] Lithium 2,2,6,6-tetramethylpiperidide.

Table 2

Reactions of 2,4-Dimethoxypyrimidine with LiTMP and Various Electrophiles

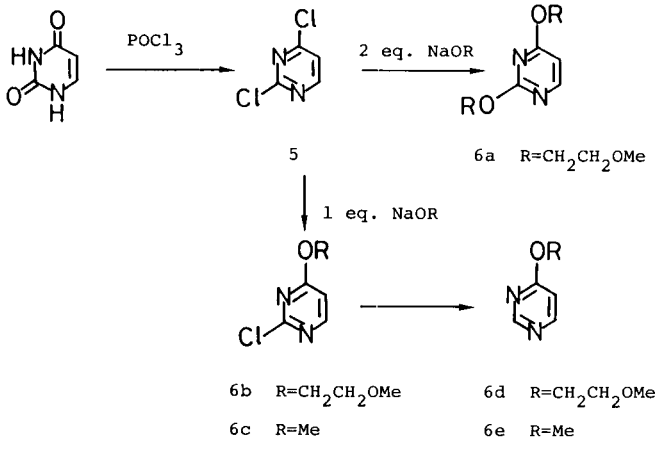
Runs	Electrophile	Product	Yield (%) [a]
1	PhCHO	**3a**	65
2	MeCHO	**3b**	44
3	CO_2	**3c** [b]	30
4	Me_2NCHO	**3d**	24
5	$ClCO_2Et$	**3e**	6
6	Me_3SiCl	**3f**	41
7	AcOEt	**3g**	4
		4	13

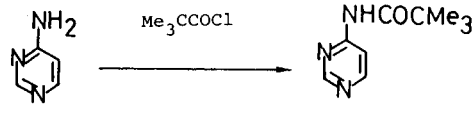
[a] Isolated yield. [b] After treatment with diazomethane.

The reactivity of *ortho*-lithiated pyrimidine **2** with various electrophiles such as acetaldehyde, carbon dioxide, *N,N*-dimethylformamide (DMF), ethyl chloroformate, trimethylsilyl chloride, and ethyl acetate was investigated, and the results are summarized in Table 2. In the reaction of ethyl acetate, 5-acetyl-2,4-dimethoxypyrimidine (**3g**) and an unexpected β-hydroxy-ester **4** were obtained in 4% and 13% yields, respectively. β-Hydroxyester **4** was presumably produced *via* the reaction of initially formed **3g** with ethyl lithioacetate.

Subsequently, in order to confirm the scope and limitation of this methodology, we investigated in various pyrimidines. These pyrimidines **6a-e** were easily obtained from uracil *via* 2,4-dichloropyrimidine (**5**). Thus, treatments of **5** with an equivalent amount of the alkoxide gave 2-chloro-4-alkoxypyrimidines **6b,c**, and two equivalents of alkoxide gave 2,4-dialkoxypyrimidine (**6a**) respectively. Dechlorination of **6b** and **6c** was achieved by the previously reported method [10], and **6f** was obtained by the reaction of 4-aminopyrimidine with pivaloyl chloride (Scheme 2).

Scheme 2



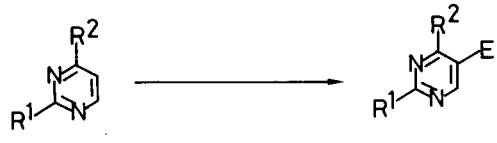


The *ortho*-directed lithiation reaction was carried out using LiTMP in ether and quenched with trimethylsilyl chloride or benzaldehyde at 0° (Scheme 3), and these results were summarized in Table 3.

Regarding the substituted moiety on the pyrimidine ring, the yields of *ortho*-substituted products of 2,4-disubstituted pyrimidines (runs 1-4) were better than those of 4-substituted pyrimidines (runs 5 and 6). These results indicate that the substituent at the 2 position of the pyrimidine ring plays an important role for the *ortho*-directed lithiation due to its inductive effect.

At the time when 4-pivaloylaminopyrimidine was lithiated, the *ortho*-substituted product was not detectable at all (run 8) and the 2-substituted product **8** was obtained in 11% yield. This result was easily understandable that the steric hindrance between the pivaloyl group with LiTMP inhibited the lithiation of the 5 position, therefore the reaction was proceeded at the 2 position, which was regarded to be the *ortho* position to both of the nitrogen atoms in the pyrimidine ring [7].

Scheme 3



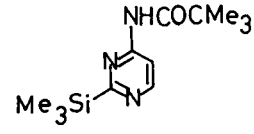


Table 3
ortho-Directed Lithiation Reactions of Various Pyrimidines with Electrophiles

Runs	Substrate	Electrophile	Product	Yield (%) [a]
1	**6a**	Me_3SiCl	**7a**	18
2	**6b**	Me_3SiCl	**7b**	15
3	**6c**	Me_3SiCl	**7c**	30
4	**6c**	PhCHO	**7d**	35
5	**6d**	Me_3SiCl	**7e**	13
6	**6d**	PhCHO	**7f**	55
7	**6e**	Me_3SiCl	**7g**	5 [b]
8	**6f**	Me_3SiCl	**7h**	0

[a] Isolated yield. [b] Reaction temperature was -70°.

EXPERIMENTAL

Measurements.

All melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270 spectrometer. Proton magnetic resonance spectra were determined on a JEOL JNM-MH-100 instrument using tetramethylsilane as the internal standard. Mass spectra were obtained with a JEOL JMS-100 instrument.

The following compounds were prepared according to the procedure described in the literature: 2,4-dimethoxypyrimidine (**1**) [7], 2-chloro-4-methoxypyrimidine (**6c**) [10], and 4-methoxypyrimidine (**6e**) [10].

2,4-Bis(2-methoxyethoxy)pyrimidine (**6a**).

This was prepared from uracil (5 g, 40 mmoles) by the same method for **1** in 55% yield (5.64 g), bp 134-136°/3 mm Hg; ir (chloroform): 1580, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 8.29 (1H, d, J = 6 Hz, C6-H), 6.49 (1H, d, J = 6 Hz, C5-H), 4.7-4.4 (4H, m, CH_2 × 2), 3.9-3.6 (4H, m, CH_2 × 2), 3.45 (6H, s, OMe × 2) ppm; ms: m/z 228 (M^+).

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.38; H, 7.11; N, 12.28.

2-Chloro-4-(2-methoxyethoxy)pyrimidine (**6b**).

This was prepared from uracil (5 g, 40 mmoles) by the same method for **6c** in 62% yield (5.24 g), bp 145-148°/28 mm Hg; ir (chloroform): 1580, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 8.36 (1H, d, J = 6 Hz, C6-H), 6.78 (1H, d, J = 6 Hz, C5-H), 4.57 (2H, dd, J = 7, 5 Hz, CH_2), 3.77 (2H, dd, J = 7, 5 Hz, CH_2), 3.42 (3H, s, OMe) ppm; ms: m/z 188, 190 (M^+).

Anal. Calcd. for $C_7H_9ClN_2O_2$: C, 44.57; H, 4.81; N, 14.86. Found: C, 44.68; H, 5.09; N, 14.87.

4-(2-Methoxyethoxy)pyrimidine (**6d**).

This was prepared from **6b** (5.24 g, 27 mmoles) by the same method for **6e** in 36% yield (1.55 g), bp 110-114°/24 mm Hg; ir (chloroform): 1580, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 8.83 (1H, s, C6-H), 8.50 (1H, d, J = 6 Hz, C6-H), 6.81 (1H, d, J = 6 Hz, C5-H), 4.59 (2H, dd, J = 6, 5 Hz, CH_2), 3.78 (2H, dd, J = 6, 5 Hz, CH_2), 3.45 (3H, s, OMe) ppm; ms: m/z 154 (M^+).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.48; H, 6.63; N, 18.25.

4-Pivaloylaminopyrimidine (**6f**).

A solution of pivaloyl chloride (390 mg, 3.2 mmoles) in chloroform (4 ml) was added dropwise over 5 minutes to an ice-cold solution of 4-aminopyrimidine (300 mg, 3.2 mmoles) and triethylamine (320 mg, 3.2 mmoles) in chloroform (20 ml). The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate (15 ml) and chloroform (150 ml). The organic layer was washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was recrystallized from hexane-chloroform to afford **6f** (410 mg, 72%), mp 115-117°; ir (chloroform): 1705, 1590, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 8.83 (1H, s, C2-H), 8.18 (1H, d, J = 6 Hz, C6-H), 7.78 (1H, s, NH), 7.74 (1H, d, J = 6 Hz, C5-H), 1.28 (9H, s, Me × 3) ppm; ms: m/z 179 (M^+).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.31; H, 7.31; N, 23.45. Found: C, 60.44; H, 7.42; N, 23.64.

General Procedure for Lithiation of Pyrimidines and Reactions with Electrophiles.

A solution of *n*-BuLi (1.6*N*, 2.6 ml, 4.2 mmoles) was added dropwise to a stirred solution of 2,2,4,4-tetramethylpiperidine (590 mg, 4.2 mmoles) at 0° under nitrogen atmosphere. The mixture was stirred for 15 minutes and then used as an ether solution of LiTMP. An ether (10 ml) solution of pyrimidine (3.8 mmoles) was added dropwise to the solution of LiTMP over a few minutes. After stirring an additional 10 minutes, a solution of an appropriate electrophile in ether (4 ml) was added. The reaction mixture was warmed slowly to room temperature, and then quenched with saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether (40 ml × 3). The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (with chloroform:ethyl acetate = 9:1 as the eluting solvent).

5-(2,4-Dimethoxypyrimidinyl)-1-phenylmethanol (**3a**).

This was prepared from **1** (500 mg, 3.6 mmoles) and benzaldehyde (420 mg, 4.0 mmoles) in 65% yield (582 mg), bp 160-165°/3 mm Hg; ir (chloroform): 3500, 1600, 1570 cm^{-1}; ^1H nmr (deuteriochloroform): 8.16 (1H, s, C6-H), 7.28 (5H, br s, Ph), 5.84 (1H, s, CH), 3.92 (6H, s, OMe × 2) ppm, OH is absent; ms: m/z 246 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.62; H, 5.75; N, 11.69.

1-[5-(2,4-Dimethoxypyrimidinyl)]ethanol (**3b**).

This was prepared from **1** (500 mg, 3.6 mmoles) and acetaldehyde (large excess) in 44% yield (290 mg) as a pale yellow oil; ir (chloroform): 3500, 1605, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 8.45 (1H, s, C6-H), 5.09 (1H, m, CH), 4.11 (3H, s, OMe), 4.03 (3H, s, OMe), 2.45 (3H, d, J = 7 Hz, Me) ppm, OH is absent; ms: m/z 184 (M^+).

Anal. Calcd. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.36; H, 6.45; N, 15.33.

Methyl 2,4-Dimethoxypyrimidine-5-carboxylate (**3c**).

This was prepared from **1** (500 mg, 3.6 mmoles) and excess solid carbon dioxide, and then treatment with ethereal diazomethane in 30% yield (145 mg), mp 91-93° (hexane-chloroform); ir (chloroform): 1730, 1595, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): 8.73 (1H, s, C6-H), 4.04 (3H, s, OMe), 3.99 (3H, s, OMe), 3.82 (3H, s, OMe) ppm; ms: m/z 198 (M^+).

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.61; H, 5.15; N, 14.31.

5-Formyl-2,4-dimethoxypyrimidine (**3d**).

This was prepared from **1** (400 mg, 2.9 mmoles) and DMF (400 mg, 5.5 mmoles) in 24% yield (115 mg), mp 120-122° (hexane) (reference [11], 123°).

Ethyl 2,4-Dimethoxypyrimidine-5-carboxylate (**3e**).

This was prepared from **1** (500 mg, 3.6 mmoles) and ethyl chloroformate (780 mg, 7.2 mmoles) in 6% yield (40 mg), mp 60-61° (petroleum ether); ir (chloroform): 1725, 1595, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): 8.76 (1H, s, C6-H), 4.32 (2H, q, J = 6 Hz, CH_2), 4.04 (3H, s, OMe), 4.00 (3H, s, OMe), 1.36 (3H, t, J = 6 Hz, Me) ppm; ms: m/z 212 (M^+).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.06; H, 5.76; N, 13.16.

2,4-Dimethoxy-5-trimethylsilylpyrimidine (**3f**).

This was prepared from **1** (500 mg, 3.6 mmoles) and trimethylsilyl chloride (780 mg, 7.2 mmoles) in 41% yield (310 mg) as an oil; ir (chloroform): 1570, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 8.21 (1H, s, C6-H), 3.94 (6H,s, OMe), 0.26 (9H, s, $SiMe_3$) ppm; ms: m/z 212 (M^+).

Anal. Calcd. for $C_9H_{16}N_2O_2Si$: C, 50.91; H, 7.60; N, 13.20. Found: C, 51.05; H, 7.64; N, 13.41.

5-Acetyl-2,4-dimethoxypyrimidine (**3g**).

This was prepared from **1** (500 mg, 3.6 mmoles) and ethyl acetate (635 mg, 7.2 mmoles) in 4% yield (25 mg), mp 82-83° (petroleum ether); ir (chloroform): 1680, 1585, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 8.82 (1H, s, C6-H), 4.08 (3H, s, OMe), 4.04 (3H, s, OMe), 2.58 (3H, s, COMe) ppm; ms: m/z 182 (M^+).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.86; H, 5.45; N, 15.31.

Ethyl 2-Hydroxy-2-(2,4-dimethoxypyrimidin-5-yl)propionate (**4**).

This was prepared from **1** (500 mg, 3.6 mmoles) and ethyl acetate (635 mg, 7.2 mmoles) in 13% yield (154 mg) as a pale yellow oil; ir (chloroform): 3500, 1715, 1595, 1570 cm^{-1}; ^1H nmr (deuteriochloroform): 8.41 (1H, s, C6-H), 4.28 (1H, br s, OH), 4.02 (2H, q, J = 7 Hz, CH_2), 3.99 (3H, s, OMe), 3.91 (3H, s, OMe), 3.16 (1H, d, J = 15 Hz, HCHCO), 2.78 (1H, d, J = 15 Hz, HCHCO), 1.55 (3H, s, Me), 1.14 (3H, t, J = 7 Hz, Me) ppm; ms: m/z 270 (M^+).

Anal. Calcd. for $C_{12}H_{18}N_2O_5$: C, 53.32; H, 6.71; N, 10.37. Found: C, 53.08; H, 6.55; N, 10.30.

2,4-Bis(2-methoxyethoxy)-5-trimethylsilylpyrimidine (**7a**).

This was prepared from **6a** (400 mg, 1.8 mmoles) and trimethylsilyl chloride (300 mg, 3.0 mmoles) in 18% yield (96 mg) as an oil; ir (chloroform): 1570, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 8.16 (1H, s, C6-H), 4.51 (4H, t, J = 5 Hz, CH_2 × 2), 3.74 (2H, t, J = 5 Hz, CH_2), 3.70 (2H, t, J = 5 Hz, CH_2), 3.42 (6H, s, OMe x 2), 3.39 (3H, s, OMe), 0.27 (9H, s, $SiMe_3$) ppm; ms: m/z 300 (M^+).

Anal. Calcd. for $C_{13}H_{24}N_2O_4Si$: C, 51.97; H, 8.05; N, 9.33. Found: C, 52.06; H, 8.12; N, 9.41.

2-Chloro-4-(2-methoxyethoxy)-5-trimethylsilylpyrimidine (**7b**).

This was prepared from **6b** (330 mg, 1.8 mmoles) and trimethylsilyl chloride (300 mg, 3.0 mmoles) in 15% yield (68 mg) as an yellow oil; ir (chloroform): 1555, 1535 cm^{-1}; ^1H nmr (deuteriochloroform): 8.26 (1H, s, C6-H), 4.49 (2H, dd, J = 5, 7 Hz, CH_2), 3.68 (2H, dd, J = 5, 7 Hz, CH_2), 3.38 (3H, s, OMe), 0.29 (9H, s, $SiMe_3$) ppm; ms: m/z 260, 262 (M^+).

Anal. Calcd. for $C_{10}H_{17}ClN_2O_2Si$: C, 46.05; H, 6.57; N, 10.74. Found: C, 46.31; H, 6.66; N, 10.92.

2-Chloro-4-methoxy-5-trimethylsilylpyrimidine (**7c**).

This was prepared from **6c** (300 mg, 2.1 mmoles) and trimethylsilyl chloride (450 mg, 4.2 mmoles) in 30% yield (135 mg) as an oil; ir (chloroform): 1550, 1530 cm^{-1}; ^1H nmr (deuteriochloroform): 8.33 (1H, s, C6-H), 3.92 (3H, s, OMe), 0.28 (9H, s, $SiMe_3$) ppm; ms: m/z 216, 218 (M^+).

Anal. Calcd. for $C_8H_{13}ClN_2OSi$: C, 44.33; H, 6.04; N, 12.93. Found: C, 44.41; H, 6.17; N, 12.88.

5-(2-Chloro-4-methoxypyrimidinyl)-1-phenylmethanol (**7d**).

This was prepared from **6c** (300 mg, 2.1 mmoles) and benzaldehyde (445 mg, 4.2 mmoles) in 35% yield (183 mg) as a pale yellow oil; ir (chloroform): 3500, 1580, 1560 cm^{-1}; ^1H nmr (deuteriochloroform): 8.40 (1H, s, C6-H), 7.28 (5H, br s, Ph), 5.84 (1H, s, CH), 4.02 (1H, br s, OH), 3.96 (3H, s, OMe) ppm; ms: m/z 250, 252 (M^+).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.18. Found: C, 57.55; H, 4.38; N, 11.03.

4-(2-Methoxyethoxy)-5-trimethylsilylpyrimidine (**7e**).

This was prepared from **6d** (300 mg, 1.9 mmoles) and trimethylsilyl chloride (410 mg, 3.8 mmoles) in 13% yield (57 mg) as an oil; ir (chloroform): 1560, 1545 cm^{-1}; ^1H nmr (deuteriochloroform): 8.81 (1H, s, C2-H), 8.47 (1H, s, C6-H), 4.57 (2H, dd, J = 5, 6 Hz, CH_2), 3.78 (2H, dd, J = 5, 6 Hz, CH_2), 3.44 (3H, s, OMe), 0.28 (9H, s, $SiMe_3$) ppm; ms: m/z 226 (M^+).

Anal. Calcd. for $C_{10}H_{18}N_2O_2Si$: C, 53.03; H, 8.01; N, 12.38. Found: C, 53.11; H, 8.12; N, 12.48.

5-[4-(2-Methoxyethoxy)pyrimidinyl]-1-phenylmethanol (**7f**).

This was prepared from **6d** (300 mg, 2.1 mmoles) and benzaldehyde (400 mg, 3.8 mmoles) in 22% yield (120 mg) as a pale yellow oil; ir (chloroform): 3500, 1575, 1555 cm^{-1}; ^1H nmr (deuteriochloroform): 8.66 (1H, s, C2-H), 8.64 (1H, s, C6-H), 7.48 (5H, br s, Ph), 6.00 (1H, s, CH), 4.68 (1H, br s, OH), 4.51 (2H, dd, J = 5, 6 Hz, CH_2), 3.63 (2H, dd, J = 5, 6 Hz, CH_2), 3.34 (3H, s, OMe) ppm; ms: m/z 260 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.49; H, 6.33; N, 10.93.

4-Methoxy-5-trimethylsilylpyrimidine (**7g**).

This was prepared from **6e** (220 mg, 2.0 mmoles) and trimethylsilyl chloride (300 mg, 3.0 mmoles) in 5% yield (18 mg) as an oil; ir (chloroform): 1560, 1550 cm^{-1}; ^1H nmr (deuteriochloroform): 8.82 (1H, s, C2-H), 8.44 (1H, s, C6-H), 3.98 (3H, s, OMe), 0.26 (9H, s, $SiMe_3$) ppm; ms: m/z 182 (M^+).

Anal. Calcd. for $C_8H_{14}N_2OSi$: C, 52.70; H, 7.75; N, 15.37. Found: C, 52.85; H, 7.79; N, 15.45.

4-Pivaloylamino-2-trimethylsilylpyrimidine (**8**).

This was prepared from **6f** (250 mg, 1.4 mmoles) and trimethylsilyl chloride (220 mg, 2.7 mmoles) in 11% yield (30 mg) as an oil; ir (chloroform): 1705, 1590, 1575 cm^{-1}; ^1H nmr (deuteriochloroform): 8.76 (1H, d, J = 5 Hz, C6-H), 8.18 (1H, br s, NH), 8.16 (1H, d, J = 5 Hz, C5-H), 1.39 (9H, s, CMe_3), 0.36 (9H, s, $SiMe_3$) ppm; ms: m/z 251 (M^+).

Anal. Calcd. for $C_{12}H_{21}N_3OSi$: C, 57.33; H, 8.42; N, 16.71. Found: C, 57.47; H, 8.51; N, 16.69.

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REFERENCES AND NOTES

[1] A part of this work was published in a preliminary communication: A. Wada, J. Yamamoto and S. Kanatomo, *Heterocycles*, **26**, 585 (1987).

[2] For reviews: J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969); H. W. Gschwend and H. R. Rodoriguez, *Org. React.*, **26**, 1 (1979); R. Beak and V. Snieckus, *Acc. Chem. Res.*, **15**, 306 (1982); N. S. Narashimhan and R. S. Mall, *Synthesis*, 957 (1983); M. Watanabe, *Yuki Gosei*

Kagaku Kyokai Shi, **41**, 728 (1983).

[3] The *ortho*-directed lithiation of heteroaromatics is limited in only the pyridine system: M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, **47**, 2101 (1982); A. I. Meyers and R. A. Gabel, *Tetrahedron Letters*, 227 (1978); *Heterocycles*, **11**, 133 (1978); *J. Org. Chem.*, **47**, 2633 (1982); G. W. Gribble and M. G. Saulnier, *Tetrahedron Letters*, **21**, 4137 (1980); A. R. Katritzky, S. R. Rastgoo and N. K. Ponkshe, *Synthesis*, 127 (1981); T. Güngör, F. Marsais and G. Quéguiner, *ibid.*, 499 (1982); F. Marsais, G. Le Nard and G. Quéguiner, *ibid.*, 235 (1982); E. J. Corey, S. G. Pyne and A. I. Schafer, *Tetrahedron Letters*, **24**, 3291 (1983); J. A. Turner, *J. Org. Chem.*, **48**, 3401 (1983); D. L. Comins and D. H. LaMunyon, *Tetrahedron Letters*, **29**, 773 (1988).

[4] T. V. Rajkumar and S. B. Binkley, *J. Med. Chem.*, **6**, 550 (1963); B. W. Langley, *J. Am. Chem. Soc.*, **78**, 2136 (1956); T. K. Liao, E. G. Podrebarac and C. C. Cheng, *ibid.*, **86**, 1869 (1964); W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966); D. M. Mulvey, R. D. Babson, S. Zawoiski and M. A. Ryder, *J. Heterocyclic Chem.*, **10**, 79 (1973); M. P. L. Caton, M. S. Grant, D. L. Pain and R. Slack, *J. Chem. Soc.*, 5467 (1965).

[5] The lithiation of 5-methylpyrimidine was reported previously but in this case the lithiated position was regarded to be the *ortho* position to the nitrogen atom in the pyrimidine ring: A. J. Clarke, S. McNamara and O. Meth-Cohn, *Tetrahedron Letters*, 2373 (1974).

[6] Very recently, Haimova *et al.*, have reported the *ortho*-directed lithiation of 2,6-dichloropyrimidine, which have two activating groups: R. Radinov, M. Haimova and E. Simova, *Synthesis*, 886 (1986).

[7] S. Gabriel and J. Colman, *Chem. Ber.*, **32**, 2921 (1899).

[8] T. Nishiwaki, *Tetrahedron*, **22**, 2401 (1966).

[9] M. Fieser and L. F. Fieser, Reagents for Organic Synthesis, Vol **4**, John Wiley and Sons, 1974, p 310.

[10] H. Yamanaka, *Chem. Pharm. Bull.*, **7**, 297 (1959).

[11] E. L. Stogryn, *J. Heterocyclic Chem.*, **11**, 251 (1974).