Synthesis of Pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones *via* Anionic Cycloaddition of Methyl 2,4-Dimethoxy-6-methyl-5-pyrimidinecarboxylate with Imines

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A new route is described for the synthesis of pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones. Treatment of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate with lithium diisopropylamine in tetrahydrofuran at −70 °C under nitrogen followed by reaction with diaryl imines afforded cycloaddition products. The cycloadducts were aromatized to the corresponding pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones by treatment with *N*-bromosuccinimide *via* a benzylic bromination-dehydrobromination sequence.

Keywords anionic cycloaddition; methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate; diaryl imine; pyrido[4,3-*d*]pyrimidin-5(6*H*)-one; aromatization; *N*-bromosuccinimide

Methods for the preparation of pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones are of considerable interest in view of the potentially significant biological activities, such as herbicidal, antihypertensive, and antiallergic activities, of these compounds.[1] Since Ismail and Wibberley[2] reported the first synthesis of pyrido[4,3-*d*]pyrimidine-5(6*H*)-one systems by the reaction of pyrano[4,3-*d*]pyrimidin-5-one with amines, several approaches have been reported by different groups.[1,3] During studies on a new synthesis of biologically useful heterocycles through anionic cyclization using benzylic carbanion species of heteroaromatics,[4] we succeeded in a synthesis of quinazolines[5] and pyrano[4,3-*d*]pyrimidines[6] *via* anionic cyclization of methyl 2,4-dimethoxy-6-methyl-5-pyrimidinecarboxylate (**1**) with olefins and aldehydes, respectively. We describe here a further application of this cyclization, using **1** as a 1,4-dipolar synthon, to a novel synthesis of pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones.

Cycloaddition of 1 with Imines Treatment of the lithium salt of **1**, generated by the deprotonation with lithium diisopropylamido (LDA) in tetrahydrofuran (THF), with benzalaniline (**2a**) at −70 °C followed by work-up at 0 °C gave the cycloadduct (**3a**) in 30% yield along with the starting material (**1**) in 27% yield. The structure of **3a** was determined on the basis of the elemental analysis and spectral data. The ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectrum showed a methine proton signal at 5.23 (dd, 1H, J=6.5 Hz, 2.5 Hz) and two methylene proton signals at 3.79 (dd, 1H, J=17, 6.5 Hz) and 3.22 ppm (dd, 1H, J=17, 2.5 Hz).

In order to examine the generality of this cyclization, the reactions with various kinds of imine derivatives, such as diaryl imines (**2**), aryl alkyl imines (**4a**, **b**), aldoxime ether (**4c**), *N*-phenyl formimidate (**5**), lactim ether (**6**), and keto alkyl imine (**7**), were also investigated. The reactions with **2b**—**k** afforded the expected cycloadducts (**3b**—**k**) in modest yields accompanied with the recovery of **1** (Chart 1). The results with **2** are summarized in Table I. None of the other imines gave the desired cycloadducts and only the starting ester (**1**) was recovered.

It is noteworthy that in the reaction of *p*-nitrobenzalaniline (**2k**), the aromatized cycloadduct (**8k**) was obtained in 39% yield. This compound was presumably produced by oxidation of the initially formed cycloadduct (**3k**) under the reaction conditions. In fact, when the reaction was quenched immediately at −70 °C, the expected cycloadduct (**3k**) and the aromatized product (**8k**) were obtained in 24 and 7% yields, respectively.

A comparison of the present results with those for the reaction with olefins[5] and aldehydes[6] indicated that the reactivity of the anion from **1** with the imines (**2**) is rather low. Recently, Akiba *et al.* reported that boron trifluoride-etherate activates the imine and the yield in the addition reaction of the alkyl anion is dramatically improved.[7] We tried this procedure, but the desired cycloaddition did not occur, and the starting ester (**1**) and imine (**2**) were recovered. In addition, an attempt to modify the basicity of the lithio species through the use of anhydrous cerium (III) chloride[8] and dialkyl aluminum chloride[9] also failed to produce the cycloadduct.

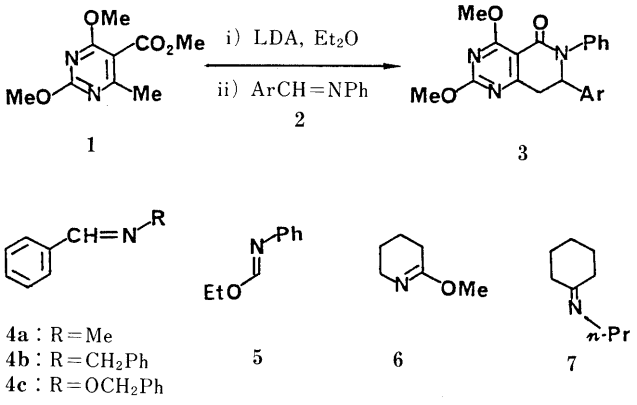
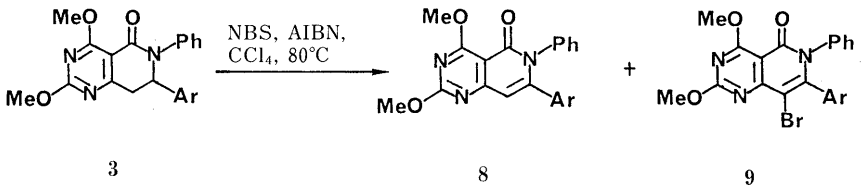


Chart 1

TABLE I. Reaction of **1** with Imines (**2**)

Run	**2** Ar		Yield **3**	Yield (%)[a]	Recovery yield **1** (%)[a]
1	C_6H_5	(**2a**)	**3a**	30	27
2	2-$MeOC_6H_4$	(**2b**)	**3b**	18	29
3	3-$MeOC_6H_4$	(**2c**)	**3c**	21	30
4	4-$MeOC_6H_4$	(**2d**)	**3d**	16	32
5	2-ClC_6H_4	(**2e**)	**3e**	27	25
6	3-ClC_6H_4	(**2f**)	**3f**	8	37
7	4-ClC_6H_4	(**2g**)	**3g**	12	35
8	2-MeC_6H_4	(**2h**)	**3h**	17	49
9	2-$NO_2C_6H_4$	(**2i**)	**3i**	11	61
10	3-$NO_2C_6H_4$	(**2j**)	**3j**	16	48
11	4-$NO_2C_6H_4$	(**2k**)	**3k**	24[b]	47[b]

a) Isolated yield. *b*) The reaction was quenched at −70 °C.



3 8 9

Chart 2

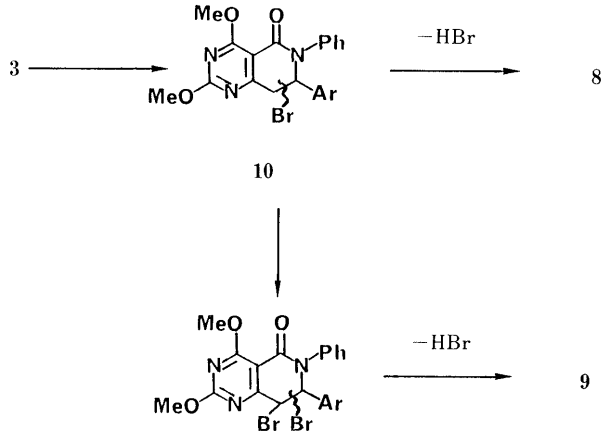


Chart 3

TABLE II. Aromatization of Cycloadducts (3)

Run	Substrate		Yield of product			
	3	Ar	8	(%)[a]	9	(%)[a]
1	**3a**	C_6H_5	**8a**	32	**9a**	41
2	**3c**	3-$MeOC_6H_4$	**8c**	44	**9c**	32
3	**3d**	4-$MeOC_6H_4$	**8d**	35	**9d**	29
4	**3e**	2-ClC_6H_4	**8e**	51	**9e**	29
5	**3g**	4-ClC_6H_4	**8g**	45	**9g**	11
6	**3h**	2-MeC_6H_4	**8h**	37	**9h**	0
7	**3i**	2-$NO_2C_6H_4$	**8i**	7	**9i**	0

a) Isolated yield.

Aromatization of the Cycloadduct Aromatization of the cycloadducts (**3**) to pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones (**8**) was successfully achieved by means of a bromination-dehydrobromination sequence according to our previous work.[6a] In contrast to dihydropyrano[4,3-*d*]pyrimidin-5-ones,[6a] treatment of **3a** with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) afforded the bromo compound (**9a**) in addition to the desired aromatized product (**8a**) in 41 and 32% yields, respectively. The former (**9a**) was readily converted to **8a** in 84% yield by hydrogenolysis over palladium on carbon (Chart 2).

The possibility of the formation of the bromide (**9a**) from the initially formed aromatized product (**8a**) was ruled out since the bromination of **8a** did not occur under the reaction conditions used. A plausible mechanism for the formation of these aromatized products (**8a** and **9a**) is shown in Chart 3. It involves initial bromination at the benzylic position of **3a** to give the monobromo intermediate (**10**), which was transformed to **8a** with the elimination of hydrogen bromide. On the other hand, further bromination of **8a**, followed by loss of hydrogen bromide from the dibromo intermediate (**11**) afforded **9a**.

In a similar fashion, on treatment of the other cycloadducts (**3**) with NBS, the aromatized pyrido[4,3-*d*]pyrimidin-5(6*H*)-ones (**8** and **9**) were obtained. These results are summarized in Table II. In the cases of **3h** and **3i**, the corresponding bromo derivatives could not be obtained, presumably due to the steric hindrance of the *ortho*-substituent to further bromination of the monobromo intermediate (**10**).

In summary, the lithium salt of **1** reacted with diaryl imines to afford cycloadducts (**3**) and this novel anionic cycloaddition reaction provides a new route for the preparation of pyrido[4,3-*d*]pyrimidin-5(6*H*)-one derivatives (**8**).

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured in $CHCl_3$ with a JASCO A-102 spectrometer, ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard, and mass spectra (MS) with a Hitachi M-80 spectrometer. Imines were prepared by removing water by azeotropic distillation from a benzene solution of aldehydes and aniline.

General Procedure for the Reaction of 1 with Imines A solution of *n*-BuLi (1.4 M in hexane solution, 1.5 ml, 2.1 mmol) was added dropwise to a stirred solution of diisopropylamine (210 mg, 2.1 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 15 min and then THF (5 ml) was added. A solution of the ester (**1**, 400 mg, 1.9 mmol) in THF (5 ml) was added dropwise to the solution of LDA over a few minutes at −70 °C. Stirring was continued for 10 min, then a THF solution of the imine (**2**, 1.9 mmol) in THF (4 ml) was added slowly. The reaction mixture was kept at −70 °C for 30 min, then warmed slowly to 0 °C, and quenched with saturated aqueous ammonium chloride (3 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (15 ml × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform–ethyl acetate (9 : 1) to afford the cycloadduct.

7,8-Dihydro-2,4-dimethoxy-6,7-diphenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3a) This was prepared from **1** (580 mg, 3.2 mmol) and benzalaniline (**2a**, 550 mg, 3.3 mmol) in 30% yield (295 mg), mp 119—121 °C (petroleum ether). IR: 1660, 1580, 1565 cm^{-1}. ^{1}H-NMR δ: 3.22 (1H, dd, J=2.5, 17 Hz, C_8-H), 3.79 (1H, dd, J=6.5, 17 Hz, C_8-H), 3.98 (3H, s, OMe), 4.11 (3H, s, OMe), 5.23 (1H, dd, J=2.5, 6.5 Hz, C_7-H), 7.22 (5H, s, Ph), 7.24 (5H, s, Ph). MS *m/z*: 361 (M^+). *Anal.* Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.84; H, 5.45; N, 11.49.

7,8-Dihydro-2,4-dimethoxy-7-(2-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3b) This was prepared from **1** (200 mg, 0.94 mmol) and 2-methoxybenzalaniline (**2b**, 280 mg, 1.3 mmol) in 18% yield (65 mg). mp 154—155.5 °C (ether). IR: 1665, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.28 (1H, dd, J=2, 19 Hz, C_8-H), 3.68 (1H, dd, J=6, 19 Hz, C_8-H), 3.81 (3H, s, OMe), 3.96 (3H, s, OMe), 4.11 (3H, s, OMe), 5.52 (1H, dd, J=2, 6 Hz, C_7-H), 6.7—7.4 (4H, m, ArH), 7.28 (5H, s, Ph). MS *m/z*: 391 (M^+). *Anal.* Calcd for $C_{22}H_{21}N_3O_4$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.72; H, 5.28; N, 10.45.

7,8-Dihydro-2,4-dimethoxy-7-(3-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3c) This was prepared from **1** (200 mg, 0.94 mmol) and 3-methoxybenzalaniline (**2c**, 220 mg, 1.1 mmol) in 21% yield

(77 mg). mp 85—87 °C (ether). IR: 1655, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.21 (1H, dd, J=2.5, 16.5 Hz, C_8-H), 3.72 (3H, s, OMe), 3.78 (1H, dd, J=6, 16.5 Hz, C_8-H), 3.98 (3H, s, OMe), 4.10 (3H, s, OMe), 5.24 (1H, dd, J=2.5, 6 Hz, C_7-H), 6.5—7.2 (4H, m, ArH), 7.28 (5H, s, Ph). MS m/z: 391 (M^+). *Anal.* Calcd for $C_{22}H_{21}N_3O_4$: C, 67.50; H, 5.41; N, 10.74. Found: C, 67.63; H, 5.34; N, 10.76.

7,8-Dihydro-2,4-dimethoxy-7-(4-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3d) This was prepared from **1** (150 mg, 0.71 mmol) and 4-methoxybenzalaniline (**2d**, 300 mg, 1.4 mmol) in 16% yield (46 mg) as a pale yellow oil. IR: 1665, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.12 (1H, dd, J=2.5, 16 Hz, C_8-H), 3.74 (3H, s, OMe), 3.76 (1H, dd, J=6, 16 Hz, C_8-H), 3.97 (3H, s, OMe), 4.10 (3H, s, OMe), 5.17 (1H, dd, J=2.5, 6 Hz, C_7-H), 6.78 (2H, d, J=9 Hz, ArH), 7.14 (2H, d, J=9 Hz, ArH), 7.26 (5H, s, Ph). High-resolution MS Calcd for $C_{22}H_{21}N_3O_4$: 391.1530. Found: 391.1508.

7,8-Dihydro-2,4-dimethoxy-7-(2-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3e) This was prepared from **1** (200 mg, 0.94 mmol) and 2-chlorobenzalaniline (**2e**, 280 mg, 1.3 mmol) in 27% yield (101 mg). mp 158—159.5 °C (ether). IR: 1660, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.32 (1H, dd, J=2, 17 Hz, C_8-H), 3.78 (1H, dd, J=7, 17 Hz, C_8-H), 3.97 (3H, s, OMe), 4.13 (3H, s, OMe), 5.58 (1H, dd, J=2, 7 Hz, C_7-H), 7.0—7.4 (4H, m, ArH), 7.26 (5H, s, Ph). MS m/z: 395, 397 (M^+). *Anal.* Calcd for $C_{21}H_{18}ClN_3O_3$: C, 63.72; H, 4.58; N, 10.62. Found: C, 63.57; H, 4.49; N, 10.60.

7,8-Dihydro-2,4-dimethoxy-7-(3-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3f) This was prepared from **1** (200 mg, 0.94 mmol) and 3-chlorobenzalaniline (**2f**, 280 mg, 1.3 mmol) in 8% yield (30 mg) as a pale yellow oil. IR: 1660, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.18 (1H, dd, J=2.5, 17 Hz, C_8-H), 3.80 (1H, dd, J=6.5, 17 Hz, C_8-H), 3.99 (3H, s, OMe), 4.11 (3H, s, OMe), 5.19 (1H, dd, J=2.5, 6.5 Hz, C_7-H), 6.9—7.3 (9H, m, ArH). High-resolution MS Calcd for $C_{21}H_{18}ClN_3O_3$: 395.1034. Found: 395.1008.

7,8-Dihydro-2,4-dimethoxy-7-(4-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3g) This was prepared from **1** (200 mg, 0.94 mmol) and 4-chlorobenzalaniline (**2g**, 280 mg, 1.3 mmol) in 12% yield (43 mg) as a pale yellow oil. IR: 1660, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.16 (1H, dd, J=2.5, 17 Hz, C_8-H), 3.77 (1H, dd, J=6.5, 17 Hz, C_8-H), 3.98 (3H, s, OMe), 4.11 (3H, s, OMe), 5.20 (1H, dd, J=2.5, 6.5 Hz, C_7-H), 7.18 (2H, d, J=8 Hz, ArH), 7.24 (2H, d, J=8 Hz, ArH), 7.27 (5H, s, Ph). High-resolution MS Calcd for $C_{21}H_{18}ClN_3O_3$: 395.1034. Found: 395.1026.

7,8-Dihydro-2,4-dimethoxy-7-(2-methylphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3h) This was prepared from **1** (210 mg, 1.0 mmol) and 2-methylbenzalaniline (**2h**, 215 mg, 1.1 mmol) in 17% yield (51 mg). mp 97—99 °C (ether). IR: 1665, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 2.29 (3H, s, Me), 3.08 (1H, dd, J=2, 17 Hz, C_8-H), 3.76 (1H, dd, J=7, 17 Hz, C_8-H), 3.97 (3H, s, OMe), 4.13 (3H, s, OMe), 5.37 (1H, dd, J=2, 7 Hz, C_7-H), 6.9—7.4 (9H, m, ArH). High-resolution MS Calcd for $C_{22}H_{21}N_3O_3$: 375.1583. Found: 375.1577.

7,8-Dihydro-2,4-dimethoxy-7-(2-nitrophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3i) This was prepared from **1** (424 mg, 2.0 mmol) and 2-nitrobenzalaniline (**2i**, 498 mg, 2.2 mmol) in 11% yield (93 mg). mp 178—184 °C (AcOEt). IR: 1670, 1590, 1570 cm^{-1}. ^{1}H-NMR δ: 3.19 (1H, dd, J=2, 17 Hz, C_8-H), 3.92 (1H, dd, J=5.5, 17 Hz, C_8-H), 3.98 (3H, s, OMe), 4.13 (3H, s, OMe), 6.04 (1H, dd, J=2, 5.5 Hz, C_7-H), 7.0—7.7 (7H, m, ArH), 8.00 (1H, dd, J=8, 2 Hz, ArH). High-resolution MS Calcd for $C_{21}H_{18}N_4O_5$: 406.1277. Found: 406.1262.

7,8-Dihydro-2,4-dimethoxy-7-(3-nitrophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3j) This was prepared from **1** (106 mg, 0.5 mmol) and 3-nitrobenzalaniline (**2j**, 124 mg, 0.55 mmol) in 16% yield (33 mg). mp 96—99 °C (AcOEt). IR: 1660, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.24 (1H, dd, J=2.5, 17 Hz, C_8-H), 3.85 (1H, dd, J=6.5, 17 Hz, C_8-H), 3.99 (3H, s, OMe), 4.12 (3H, s, OMe), 5.37 (1H, dd, J=2.5, 6.5 Hz, C_7-H), 7.0—8.13 (9H, m, ArH). High-resolution MS Calcd for $C_{21}H_{18}N_4O_5$: 406.1277. Found: 406.1286.

7,8-Dihydro-2,4-dimethoxy-7-(4-nitrophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (3k) and 2,4-Dimethoxy-7-(4-nitrophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8k) i) These were prepared from **1** (210 mg, 1.0 mmol) and 4-nitrobenzalaniline (**2k**, 249 mg, 1.1 mmol) by quenching at −70 °C.

3k: 24% yield (90 mg). mp 117—121 °C (AcOEt). IR: 1660, 1580, 1560 cm^{-1}. ^{1}H-NMR δ: 3.19 (1H, dd, J=2.5, 17 Hz, C_8-H), 3.82 (1H, dd, J=6, 17 Hz, C_8-H), 3.99 (3H, s, OMe), 4.12 (3H, s, OMe), 5.34 (1H, dd, J=2.5, 6 Hz, C_7-H), 7.1—7.3 (5H, m, ArH), 7.45 (2H, d, J=9 Hz, ArH), 8.16 (2H, d, J=9 Hz, ArH). High-resolution MS Calcd for $C_{21}H_{18}N_4O_5$: 406.1277. Found: 406.1281.

8k: 7% yield (26 mg). mp 117—121 °C (AcOEt–*n*-hexane). IR: 1670, 1620, 1590 cm^{-1}. ^{1}H-NMR δ: 4.10 (3H, s, OMe), 4.13 (3H, s, OMe), 6.51 (1H, s, C_8-H), 7.0—7.3 (5H, m, ArH), 7.37 (2H, d, J=8 Hz, ArH), 8.02 (2H, d, J=8 Hz, ArH). High-resolution MS Calcd for $C_{21}H_{16}N_4O_5$: 404.1120. Found: 404.1122.

ii) The aromatized cycloadduct (**8k**) was prepared from **1** (210 mg, 1.0 mmol) and 4-nitrobenzalaniline (**2k**, 250 mg, 1.1 mmol) by quenching at room temperature in 39% yield (165 mg). This was identical with the sample obtained in i).

General Procedure for Aromatization of the Cycloadduct A mixture of a cycloadduct (**3**, 0.50 mmol), NBS (90 mg, 0.55 mmol), and AIBN (5 mg, 0.03 mmol) in CCl_4 (15 ml) was refluxed for 2 h. After cooling, the reaction mixture was poured into ice-water (30 ml) and extracted with $CHCl_3$ (30 ml). The extract was successively washed with aqueous 10% $Na_2S_2O_3$ (40 ml), and brine (40 ml), and then dried over Na_2SO_4. This solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with dichloromethane–ethyl acetate (19 : 1) to afford **9** and **8** from the first and second fractions, respectively.

2,4-Dimethoxy-6,7-diphenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8a) and 8-Bromo-2,4-dimethoxy-6,7-diphenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (9a) These were prepared from **3a** (70 mg, 0.20 mmol) and NBS (46 mg, 0.28 mmol).

8a: 32% yield (22 mg). mp 228—229 °C (dichloromethane–petroleum ether). IR: 1670, 1620, 1570, 1545 cm^{-1}. ^{1}H-NMR δ: 4.03 (3H, s, OMe), 4.11 (3H, s, OMe), 6.47 (1H, s, C_8-H), 6.9—7.5 (10H, m, Ph × 2). MS m/z: 359 (M^+). *Anal.* Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.41; H, 4.65; N, 11.88.

9a: 41% yield (35 mg). mp 275—277 °C (petroleum ether). IR: 1670, 1620, 1580, 1540 cm^{-1}. ^{1}H-NMR δ: 4.12 (6H, s, OMe × 2) 6.7—7.4 (10H, m, Ph × 2). MS m/z: 437, 439 (M^+). *Anal.* Calcd for $C_{21}H_{16}BrN_3O_3$: C, 57.55; H, 3.68; N, 9.59. Found: C, 57.62; H, 3.65; N, 9.34.

2,4-Dimethoxy-7-(3-methoxyphenyl)-6-phenylpyrido[4,3-*d*]-pyrimidin-5(6*H*)-one (8c) and 8-Bromo-2,4-dimethoxy-7-(3-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (9c) These were prepared from **3c** (45 mg, 0.11 mmol) and NBS (24 mg, 0.13 mmol).

8c: 44% yield (19 mg). mp 179—181 °C (dichloromethane–petroleum ether). IR: 1660, 1620, 1575, 1540 cm^{-1}. ^{1}H-NMR δ: 3.64 (3H, s, OMe), 4.09 (3H, s, OMe), 4.16 (3H, s, OMe), 6.56 (1H, s, C_8-H), 6.6—7.4 (9H, m, ArH). MS m/z: 389 (M^+). *Anal.* Calcd for $C_{22}H_{19}N_3O_4$: C, 67.85; H, 4.92; N, 10.79. Found: C, 67.71; H, 4.81; N, 10.77.

9c: 32% yield (17 mg). mp 153—155 °C (petroleum ether). IR: 1660, 1610, 1570, 1535 cm^{-1}. ^{1}H-NMR δ: 3.73 (3H, s, OMe), 4.15 (3H, s, OMe), 4.17 (3H, s, OMe), 6.7—7.3 (9H, m, ArH). MS m/z: 467, 469 (M^+). *Anal.* Calcd for $C_{22}H_{18}BrN_3O_4$: C, 56.42; H, 3.87; N, 8.97. Found: C, 56.39; H, 3.91; N, 8.76.

2,4-Dimethoxy-7-(4-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8d) and 8-Bromo-2,4-dimethoxy-7-(4-methoxyphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (9d) These were prepared from **3d** (22 mg, 0.056 mmol) and NBS (12 mg, 0.067 mmol).

8d: 35% yield (8 mg). mp 53—54 °C (dichloromethane–petroleum ether). IR: 1665, 1615, 1570, 1540 cm^{-1}. ^{1}H-NMR δ; 3.73 (3H, s, OMe), 4.09 (3H, s, OMe), 4.15 (3H, s, OMe), 6.52 (1H, s, C_8-H), 6.68 (2H, d, J=8.5 Hz, ArH), 6.9—7.3 (5H, m, ArH), 7.07 (2H, d, J=8.5 Hz, ArH). High-resolution MS Calcd for $C_{22}H_{19}N_3O_4$: 389.1374. Found: 389.1374.

9d: 29% yield (7.5 mg). mp 201—203 °C (petroleum ether). IR: 1665, 1610, 1575, 1535 cm^{-1}. ^{1}H-NMR δ: 3.73 (3H, s, OMe), 3.99 (3H, s, OMe), 4.16 (3H, s, OMe), 6.72 (2H, d, J=9 Hz, ArH), 6.9—7.4 (7H, m, ArH). High-resolution MS Calcd for $C_{22}H_{18}BrN_3O_4$: 467.0481. Found: 467.0470.

2,4-Dimethoxy-7-(2-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8e) and 8-Bromo-2,4-dimethoxy-7-(2-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (9e) These were prepared from **3e** (33 mg, 0.08 mmol) and NBS (18 mg, 0.10 mmol).

8e: 51% yield (17 mg). mp 216—218 °C (dichloromethane–petroleum ether). IR: 1665, 1620, 1575, 1545 cm^{-1}. ^{1}H-NMR δ: 4.09 (3H, s, OMe), 4.16 (3H, s, OMe), 6.49 (1H, s, C_8-H), 7.0—7.4 (9H, m, ArH). MS m/z: 393, 395 (M^+). *Anal.* Calcd for $C_{21}H_{16}ClN_3O_3$: C, 64.04; H, 4.10; N, 10.67. Found: C, 64.15; H, 4.11; N, 10.71.

9e: 29% yield (12 mg). mp 263—265 °C (petroleum ether). IR: 1665, 1605, 1570, 1535 cm^{-1}. ^{1}H-NMR δ: 4.17 (6H, s, OMe × 2), 6.9—7.4 (9H, m, ArH). MS m/z: 471, 473 (M^+). *Anal.* Calcd for $C_{21}H_{15}BrClN_3O_3$: C, 53.35; H, 3.20; N, 8.89. Found: C, 53.39; H, 3.37; N, 8.71.

2,4-Dimethoxy-7-(4-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8g) and 8-Bromo-2,4-dimethoxy-7-(4-chlorophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (9g) These were prepared from **3g**

(25 mg, 0.06 mmol) and NBS (14 mg, 0.07 mmol).

8g: 45% yield (11 mg). mp 188—190 °C (dichloromethane–petroleum ether). IR: 1665, 1620, 1575, 1540 cm^{-1}. ^{1}H-NMR δ: 4.08 (3H, s, OMe), 4.15 (3H, s, OMe), 6.51 (1H, s, C_8-H), 6.9—7.4 (9H, m, ArH). High-resolution MS Calcd for $C_{21}H_{16}ClN_3O_3$: 393.0881. Found: 393.0879.

9g: 11% yield (3.3 mg). mp 242—246 °C (petroleum ether). IR: 1665, 1600, 1575, 1535 cm^{-1}. ^{1}H-NMR δ: 4.16 (3H, s, OMe), 4.18 (3H, s, OMe), 6.9—7.4 (9H, m, ArH). High-resolution MS Calcd for $C_{21}H_{15}BrClN_3O_3$: 470.9984. Found: 470.9978.

2,4-Dimethoxy-7-(2-methylphenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8h) This was prepared from **3h** (41 mg, 0.11 mmol) and NBS (23 mg, 0.13 mmol) in 37% yield (15 mg). mp 111—114 °C (dichloromethane–petroleum ether). IR: 1665, 1620, 1575, 1540 cm^{-1}. ^{1}H-NMR δ: 2.20 (3H, s, Me), 4.09 (3H, s, OMe), 4.16 (3H, s, OMe), 6.42 (1H, s, C_8-H), 6.9—7.4 (9H, m, ArH). High-resolution MS Calcd for $C_{22}H_{19}ClN_3O_3$: 373.1424. Found: 373.1418.

2,4-Dimethoxy-7-(2-nitrophenyl)-6-phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-one (8i) This was prepared from **3i** (24 mg, 0.06 mmol) and NBS (21 mg, 0.12 mmol) in 7% yield (2 mg). mp 114—116 °C (dichloromethane–petroleum ether). IR: 1665, 1620, 1575, 1540 cm^{-1}. ^{1}H-NMR δ: 4.08 (3H, s, OMe), 4.17 (3H, s, OMe), 6.46 (1H, s, C_8-H), 6.8—7.4 (8H, m, ArH), 7.89 (1H, d, J=8 Hz, ArH). High-resolution MS Calcd for $C_{21}H_{16}N_4O_5$: 404.1119. Found: 404.1097.

Hydrogenolysis of 9a A mixture of **9a** (4.6 mg, 0.01 mmol) and 10% Pd–C (15 mg) in EtOH (4 ml) was stirred for 2 h under H_2. After removal of Pd–C by filtration, the filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with ethyl acetate–*n*-hexane (1 : 2) to afford **8a** (3.2 mg, 84%). This was identical with an authentic sample obtained by the aromatization of **3a**.

References and Notes

1) Various patents have been applied for, *e.g.*, N. Kihara, T. Ishida, S. Isayama, T. Ishitoku, H. Tan, and K. Takahashi, PCT Int. Appl. WO 86 01 207 (1986) [*Chem. Abstr.*, **105**, 24277*h* (1986)]; K. Yokoyama, K. Kato, T. Kitahara, H. Ohno, T. Nishina, A. Awaya, T. Nakano, K. Watanabe, S. Saruta, and M. Kumakura, Eur. Pat. Appl. EP 188 094 (1986) [*Chem. Abstr.*, **105**, 208919*a* (1986)]; K. Go, Y. Kurimoto, and N. Kitamura, Eur. Pat. Appl. EP 244 352 (1987) [*Chem. Abstr.*, **108**, 75423*x* (1988)].
2) A. G. Ismail and D. G. Wibberley, *J. Chem. Soc.* (*C*), **1968**, 2706.
3) G. Zigeuner, W.-B. Lintschinger, A. Fuchsgruber, and K. Kollmann, *Monatsh. Chem.*, **107**, 155 (1976); M. Balogh, I. Hermecz, Z. Mészáros, K. Simon, L. Pusztay, G. Horváth, and P. Dvortsák, *J. Heterocycl. Chem.*, **17**, 359 (1980); T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 2410 (1982); A. Kumar, H. Ila, and H. Junjappa, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 857.
4) Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, **25**, 309 (1984); Y. Kita, S. Mohri, T. Tsugoshi, H. Maeda, and Y. Tamura, *Chem. Pharm. Bull.*, **33**, 4723 (1985); Y. Tamura, M. Kirihara, M. Sasho, S. Akai, J. Sekihachi, R. Okunaka, and Y. Kita, *J. Chem. Soc., Chem. Commun.*, **1987**, 1474; J. E. Macor, K. Ryan, and M. E. Newman, *J. Org. Chem.*, **54**, 4785 (1989).
5) A. Wada, H. Yamamoto, and S. Kanatomo, *Heterocycles*, **27**, 1345 (1988).
6) *a*) A. Wada and S. Kanatomo, *Synthesis*, **1989**, 316; *b*) *Idem*, *J. Heterocycl. Chem.*, **27**, 1899 (1990).
7) M. Wada, Y. Sakurai, and K. Akiba, *Nippon Kagaku Kaishi*, **1985**, 295; *idem*, *Tetrahedron Lett.*, **25**, 1083 (1984).
8) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984); S. E. Denmark, T. Weber, and D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987).
9) L. S. Liebeskind, M. E. Welker, and V. Goedken, *J. Am. Chem. Soc.*, **106**, 441 (1984); M. Wada, H. Aiura, and K. Akiba, *Tetrahedron Lett.*, **28**, 3377 (1987).