Studies on Fused Pyrimidine Derivatives. Part 13.[1] Thermal Ene Reaction of 6-(Alk-2-enylamino)-5-[(substituted imino)methyl]-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones leading to Pyrimido[4,5-*b*]azepines

Tomonori Inazumi,[a] Etsuko Harada,[a] Takashi Mizukoshi,[a] Yoshiaki Kuroki,[a] Akikazu Kakehi[b] and Michihiko Noguchi*[,a]

[a] *Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755, Japan*

[b] *Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan*

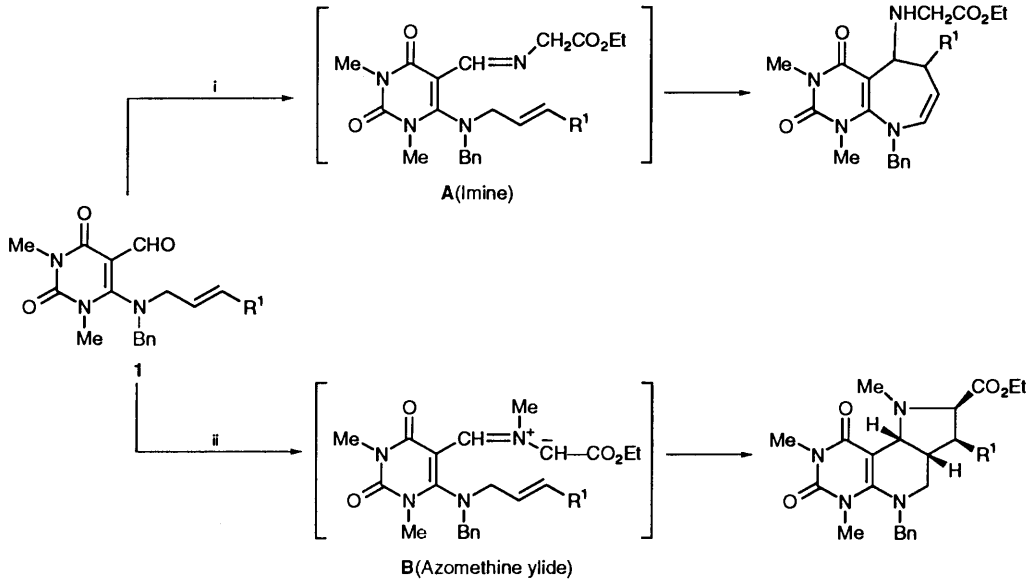
6-(Alk-2-enylamino)-1,3-dimethyl-5-[(substituted imino)methyl]pyrimidine-2,4(1*H*,3*H*)-diones, obtained from 6-(alk-2-enylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **1** and primary amines, participate in the intramolecular ene reaction (Type III) leading to pyrimido[4,5-*b*]azepine derivatives.

In the preceding paper,[1] we reported an interesting cyclisation of 6-(alk-2-enylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **1** with *N*-unsubstituted amino acid esters leading to pyrimido[4,5-*b*]azepine derivatives. On the other hand, a similar reaction of formyl diones **1** with *N*-substituted amino acid esters afforded the ordinary cyclisation products derived from azomethine ylide intermediates **B** (Scheme 1). The imine **A**, formed by the condensation of compound **1** with *N*-unsubstituted amino acid esters, was considered as an intermediary product of this cyclisation. A similar type of reaction profile was observed in the decarboxylative condensation of compounds **1** with *N*-unsubstituted and *N*-substituted amino acids. However, the mechanistic elucidation for the cyclisation was limited for the following reasons; (1) in every case imine **A** has not been characterised as yet; (2) the reaction of compounds **1** with *N*-unsubstituted amino acids was performed sluggishly. Prolonged heating of reaction mixtures consequently provided a considerable formation of unidentified products including polymeric materials; (3) the reaction of compounds **1** with *N*-unsubstituted amino acid esters gave pyrimidoazepine derivatives in excellent yields. However, most of the amino acid esters were obtained by treatment of the corresponding hydrochlorides with a slight excess of the base *in situ*. This resulted in an ambiguity in the discussion of the reaction conditions (acidic, basic or neutral?).

In order to elucidate the pathway and to extend the scope of this cyclisation, we examined the reaction of formyl diones **1** with primary and secondary amines **2**. This paper describes the successful utilisation of the cyclisation from **1** and primary amines and the confirmation of an imine as an intermediate. An intramolecular ene process for this cyclisation will be also described.

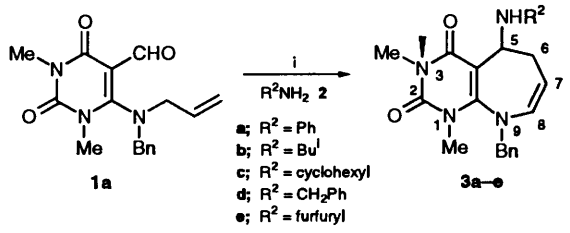
Results and Discussion

Reaction of 6-(*N*-allylbenzylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1a** with aniline **2a** in toluene under reflux for 5 h afforded 5-anilino-9-benzyl-1,3-dimethyl-6,9-dihydro-5*H*-pyrimido[4,5-*b*]azepine-2,4(1*H*,3*H*)-dione **3a** in quantitative yield. The structure of compound **3a** was confirmed on the basis of its elemental analysis and spectral data compared with those related compounds.[1] The effect of the solvent utilised in the cyclisation was also examined; heating of substrates **1a** and **2a** in 1,4-dioxane (5 h; quantitatively), in



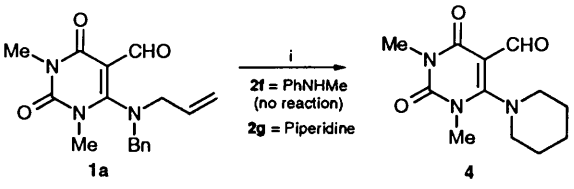
Scheme 1 *Reagents and conditions:* i, $H_2NCH_2CO_2Et$, toluene, reflux; ii, $MeNHCH_2CO_2Et$, toluene, reflux

benzene (24 h; 96%), and in acetonitrile (55 h; 93%) gave compound **3a** in satisfactory yields. Similar reactions of **1a** with isobutyl- (**2b**), cyclohexyl- (**2c**), benzyl- (**2d**), and furfuryl-amine (**2e**) gave pyrimidoazepines **3b–e** in good to excellent yields (Scheme 2). These results are summarised in Table 1.



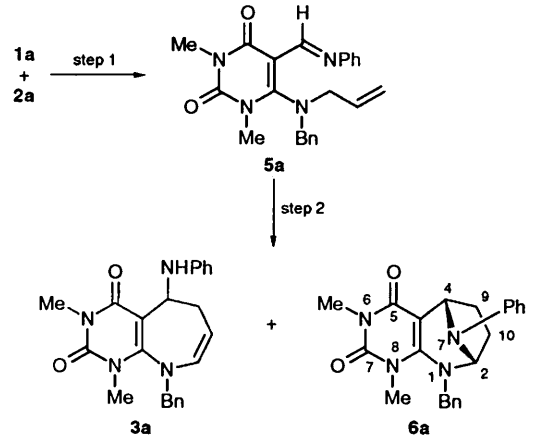
Scheme 2 *Reagents and conditions:* i, R^2NH_2 **2**, toluene, reflux

The reaction of compound **1a** with secondary amines, *N*-methylaniline **2f** and piperidine **2g**, was also examined; the former reaction resulted in the recovery of starting materials. The replacement of the amino moiety at the 6-position was observed in the latter case, leading to 5-formyl-1,3-dimethyl-6-piperidinopyrimidine-2,4(1*H*,3*H*)-dione **4** (Scheme 3).



Scheme 3 *Reagent and conditions:* i, piperidine **2g**, toluene, reflux

These findings implied that the use of primary amines, including *N*-unsubstituted α-amino acid derivatives, was requisite for construction of the pyrimidoazepine products. From the results in the preceding paper,[1] we suggested the intermediacy of the imine **5**, formed by the condensation of substrate **1a** and primary amines **2a–e**, in the azepine-ring cyclisation. Imine **5**, however, could not be obtained as a product in the above reaction runs. Therefore, we attempted to detect the imine as intermediate; on storage of a benzene solution of substrates **1a** and **2a** at room temperature for 12 h, imine **5a** was formed in 72% yield together with unchanged starting materials **1a** and **2a**. The reaction mixture was heated under reflux for 20 h to give compound **3a** in 93% yield (Scheme 4). Although the formation of imine intermediate **5a** in acetonitrile under similar conditions was slower than that in benzene, an apparent solvent effect in the conversion of imine **5a** into bicycle **3a** was not found in either solvent. The use of toluene-*p*-sulfonic acid (PTSA) as a dehydrating catalyst facilitated both the imine formation and the cyclisation, and afforded a mixture of compound **3a** and the 2,4-ethano-pyrimido[4,5-*d*]pyrimidine **6a** (Table 2).



Scheme 4 Intermediary of imine **5a** in the preparation of bicycle **3a** from starting materials **1a** and **2a**

Two diastereoisomeric pyrimidoazepine derivatives were formed by the reaction of 6-{*N*-benzyl-[(*E*)-but-2-enylamino]}-**1b** and 6-{*N*-benzyl[(*E*)-cinnamyl]amino}-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1c** with *N*-unsubstituted amino acid derivatives.[1] However, the stereochemistry between positions 5 and 6 in the pyrimido[4,5-*b*]azepine products could not be established.

Our next concern, therefore, was directed toward the stereoselectivity of the cylisation. The reactions of formyl diones **1b**, **1c**, and 6-[(*E*)-*N*-benzyl-3-(ethoxycarbonyl)prop-2-enylamino] substrate **1d** with primary amine **2a** and/or **2b** in some solvents were examined (Scheme 5). Pyrimido[4,5-*b*]azepines **7a** and **7b**, **8a** and **8b**, and **9a** were formed as inseparable mixtures of two isomers in the reaction of formyl dione **1b** with primary amines **2a** and **2b**, formyl dione **1c** with amines **2a** and **2b**, and formyl ester **1d** with amine **2a**, respectively (Table 3). The structures of these products were established by elaborate analyses of their ^1H NMR spectra.

The isomers could be easily distinguished from each other by the signal patterns of olefin protons at the 7-position; those of the major products were observed as double double doublets (J ~ 2, 2 and 9 Hz), while those of the minor products were observed as double doublets (J ~ 6 and 9 Hz). The methine protons at the 5-position of both isomers were observed between δ 3.4 and 5.9 as broad signals or as double doublet with small coupling constants (J < 3 Hz) after the treatment of deuterioxide. Therefore, the configurations between the 5-

Table 1 Reaction of formyl dione **1a** with primary amines R^2NH_2 **2**

Run	R^2	(*T*/h) Time	Products (Yield[a]/%)
1	**a** Ph	5	**3a** (quant)
2	**b** Bu^i	3	**3b** (98)
3	**c** Cyclohexyl	1	**3c** (90)
4	**d** CH_2Ph	6	**3d**[b] (quant)
5	**e** Furfuryl	26	**3e** (78)

[a] Isolated yield. [b] Known compound. See ref. 1.

Table 2 Reaction of compound **1a** with aniline **2a**

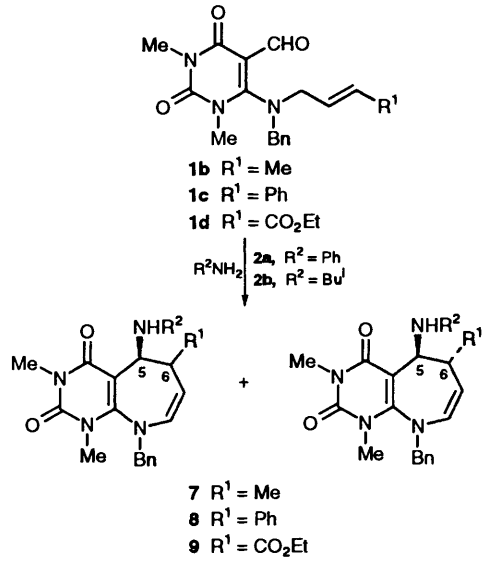
Run	Solvent	PTSA	Step 1 time (*t*/h)	Proportions[a] of **1a**:**5a**:**3a**	Step 2 time (*t*/h)	Yield[b] of products (%)	Ratio[a] of **3a**:**6a**
1	Benzene	–	12	28:72:0	20	93	100:0
2	Benzene	+	10	14:72:14	8	73	24:76
3	MeCN	–	12	61:39:0	20	90	100:0
4	MeCN	+	10	17:72:11	8	87	44:56

[a] Determined by the ^1H NMR spectra of the mixtures. [b] Isolated yield.

Table 3 Reaction of formyl diones **1b–d** with primary amines **2a** and **2b**

Run	R^1	R^2	Solvent	Time (t/h)	Products (Yield[a]:%)	Ratio[b] *cis*:*trans*
1	Me	Ph	toluene	5	**7a** (92)	88:12
2	Me	Ph	benzene	12	**7a** (85)	88:12
3	Me	Ph	MeCN	48	**7a** (92)	90:10
4	Me	Bu^i	toluene	5	**7b** (78)	81:19
5	Ph	Ph	toluene	5	**8a** (86)	66:34
6	Ph	Bu^i	toluene	5	**8b** (85)	74:26
7	Ph	Bu^i	benzene	15	**8b** (96)	74:26
8	Ph	Bu^i	MeCN	48	**8b** (86)	74:26
9	CO_2Et	Ph	toluene	5	**9a** (72)	90:10

[a] Isolated yield. [b] Determined by the ^1H NMR spectra of the mixtures.



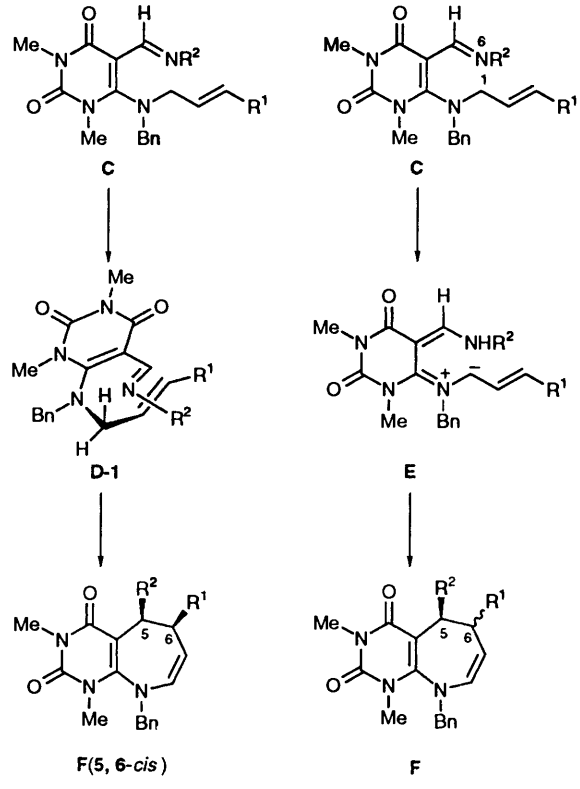
Scheme 5 *Reagents:* i, R^2NH_2 (**2a**, R^2 = Ph; **2b**, R^2 = Bu^i)

and 6-position could not be determined solely on the basis of their coupling constants.

The signal patterns of products **7** and **8** were available to the structure determinations; the methine protons at the 5-position of the minor products were observed at higher field ($\Delta\delta$ > 0.8 ppm) than those of the major products due to the shielding effect of the methyl or phenyl group at the 6-position. In product **8b**, the protons assigned to the isobutylamino group at the 5-position of the major products were shifted to higher field than those of the minor products, also due to the phenyl group at the 6-position. From these findings, the stereochemistry at the 6- and 5-position of the major products was deduced to be *cis* and that of the minor ones to be *trans*, respectively.

cis-Selectivity in the products might refer to the nature of this cyclisation. The electronic features of the substituents R^1 (*i.e.*, methyl group for compound **1b** and ethoxycarbonyl group for compound **1d**) at the alkenylamino moiety provided little effect on the selectivity. The *cis*-selectivity declined with increasing bulk of both substituents of the amine and alkenyl moieties.

For construction of the azepine ring from the imine **C**, two plausible pathways are demonstrated in Scheme 6. The first one is an intramolecular ene reaction (so-called intramolecular Type III reaction)[2a] in **C**. Another is a 1,7-electrocyclic reaction[3] of ylide intermediate **E**, which is formed by a 1,6-shift of the allylic proton adjacent to the amino nitrogen.



Scheme 6

The generation of 1,5-dipoles by a similar 1,6-hydrogen shift of (1-pyrrolidino)buta-1,3-dienes and their subsequent electrocyclic ring closure leading to pyrrolizines is known.[4] Therein, the rate of the 1,6-hydrogen shift and the stereoselectivity of the cyclisation process were substantially dependent upon the polarity of the solvent used. In the present work, the cyclisation leading to azepines exhibited no apparent solvent effects on its stereoselectivity. The reaction of 5-formyl-1,3-dimethyl-6-piperidinopyrimidine-2,4(1*H*,3*H*)-dione **4** with (or without) aniline **2a** in refluxing toluene gave no cyclisation products, due to the 1,5-dipole. From these findings, we propose a concerted ene-reaction-like mechanism for this construction of an azepine ring.

In order to obtain a better understanding of the origin of the stereoselectivity, the transition state **D** in the concerted ene process was investigated by utilising molecular models. Owing to the highly ordered transition state only a boat-shaped one (**D-1**) seems to be possible, which affords the 5,6-*cis* azepine ring system **F** (Scheme 6). We do not as yet have a good explanation

for the concerted process leading to 5,6-*trans*-azepine ring formation.

Few examples of Type III reactions have been reported so far[2a] and thermal ene reactions utilising imine enophiles[5] are also relatively rare compared with those of carbonyl enophiles. It should be emphasised that these thermal ene reactions of 6-(alk-2-enylamino)-5-[(substituted imino)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **C** proceed easily under mild conditions. We suggest that the electronic features of pyrimidine-2,4(1*H*,3*H*)-dione systems are responsible for these convenient ene reactions. Further investigations on the reaction pathway are in progress and some examples of this cyclisation will be reported in due course.

Experimental

For general details of apparatus and procedures, see the preceding paper.[1]

Splitting patterns in ^{1}H NMR spectra are indicated as s, singlet; d, doublet; m, multiplet; br, broad signal; and ov, overlapping with each other.

Reaction of Formyl Dione **1a** *with Aniline* **2a**; *Typical Procedure*.—A solution of compound **1a** (0.366 g, 1.17 mmol) and aniline **2a** (0.12 cm^3, 1.32 mmole) in toluene (5 cm^3) was heated under reflux for 5 h. The mixture was concentrated to dryness. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (4:1) as eluent to give compound **3a** (0.455 g, quantitatively).

5-*Anilino*-9-*benzyl*-1,3-*dimethyl*-6,9-*dihydro*-5H-*pyrimido*-[4,5-b]*azepine*-2,4(1H,3H)-*dione* **3a** was obtained as prisms from ethanol; m.p. 222–224 °C (Found: C, 71.2; N, 6.3; N, 14.3. $C_{23}H_{24}N_4O_2$ requires C, 71.11; H, 6.23; N, 14.42%); ν_{max}/cm^{-1} 3310 (NH), 1695 and 1630 (CO); δ_H(270 MHz) 2.46 (2 H, m, 6-H$_2$), 3.39 and 3.45 (each 3 H, each s, 1- and 3-Me), 3.65 (1 H, br, NH; exchanged with D_2O), 4.31 and 4.25 (each 1 H, each d, *J* 14.0, C*H*$_2$Ph), 4.74 (1 H, br, 5-H), 5.32 (1 H, br, 7-H), 5.97 (1 H, br d, *J* 9.9, 8-H) and 6.25, 6.61 and 7.0–7.4 (total 10 H, Ph); δ_C(67 MHz) 28.6 (1-Me), 32.7 (C-6), 35.5 (3-Me), 45.5 (*C*H$_2$Ph), 58.2 (C-5), 106.7, 108.0 (C-7 and -4a), 113.3, 117.0, 128.7, 129.0, 129.3, 129.8, 130.0, 135.2 and 146.4 (C-8 and Ph C), 152.2 (C-9a), 153.0 (C-2) and 162.6 (C-4); *m*/*z* 388 (M$^+$).

9-*Benzyl*-5-*isobutylamino*-1,3-*dimethyl*-6,9-*dihydro*-5H-*pyrimido*[4,5-b]*azepine*-2,4(1H,3H)-*dione* **3b** was obtained as needles from hexane–ethyl acetate; m.p. 150–152 °C (Found: C, 68.5; H, 7.6; N, 15.3. $C_{21}H_{28}N_4O_2$ requires C, 68.45; H, 7.66; N, 15.21%); ν_{max}/cm^{-1} 3310 (NH), 1700 and 1630 (CO); δ_H(270 MHz) 0.71 and 0.75 (each 3 H, each d, *J* 6.6, CH*Me*$_2$), 1.35 (1 H, m, C*H*Me$_2$), 1.95 (1 H, ov, NH), 1.97 (2 H, ov, NHC*H*$_2$), 2.35 (2 H, ov, 6-H$_2$), 3.36 and 3.47 (each 3 H, each s, 1- and 3-Me), 4.25 and 4.33 (each 1 H, each d, *J* 14.0, C*H*$_2$Ph), 4.3 (1 H, br, 5-H), 4.76 (1 H, ddd, *J* 4.8, 9.2 and 9.5, 7-H), 5.89 (1 H, ddd, *J* 1.5, 1.8, and 9.5, 8-H) and 7.2–7.4 (5 H, Ph); δ_C(67 MHz) 20.3 and 20.8 (CH*Me*$_2$), 28.1 (1-Me), 28.5 (*C*HMe$_2$), 32.6 (C-6), 35.2 (3-Me), 50.4 (*C*H$_2$Ph), 55.7 (NCH$_2$), 58.1 (C-5), 108.0 and 108.6 (C-7 and -4a), 128.5, 128.6, 128.9, 129.1 and 135.4 (C-8 and Ph C), 151.2 (C-9a), 153.2 (C-2) and 162.9 (C-4); *m*/*z* 368 (M$^+$).

9-*Benzy*-5-*cyclohexylamino*-6,9-*dihydro*-5H-*pyrimido*[4,5-b]-*azepine*-2,4(1H,3H)-*dione* **3c** was obtained as prisms from hexane–benzene; m.p. 130–132 °C (Found: C, 70.3; H, 7.7; N, 14.3. $C_{23}H_{30}N_4O_2$ requires C, 70.02; H, 7.67; N, 14.2%); ν_{max}/cm^{-1} 3310 (NH), 1695 and 1635 (CO); δ_H(270 MHz) 0.8, 1.0–1.2, 1.4–1.7 and 2.15 (total 12 H, cyclohexyl-H and NH), 2.30 (2 H, ov, 6-H$_2$), 3.35 and 3.46 (each 3 H, each s, 1- and 3-Me), 4.27 and 4.39 (each 1 H, each d, *J* 14.0, C*H*$_2$Ph), 4.6 and 4.8 (total 2 H, ov, 5- and 7-H), 5.90 (1 H, ddd, *J* 1.5, 1.8 and 9.9, 8-H) and 7.2–7.4 (5 H, Ph); δ_C(67 MHz) 25.1, 25.2, 26.1, 33.2, 33.4 and 54.1 (cyclohexyl C), 28.5 (1-Me), 31.4 (C-6), 35.7 (3-Me), 46.6 (*C*H$_2$Ph), 58.0 (C-5), 107.2 and 107.4 (C-7 and -4a), 128.6, 129.2 and 135.3 (C-8 and Ph C), 151.7 (C-9a), 153.2 (C-2) and 162.7 (C-4); *m*/*z* 394 (M$^+$).

9-*Benzyl*-5-*furfurylamino*-1,3-*dimethyl*-6,9-*dihydro*-5H-*pyrimido*[4,5-b]*azepine*-2,4(1H,3H)-*dione* **3e** was obtained as prisms from hexane–benzene; m.p. 121–122 °C (Found: C, 67.2; H, 6.1; N, 14.0. $C_{22}H_{24}N_4O_3$ requires C, 67.33; H, 6.16; N, 14.28%); ν_{max}/cm^{-1} 3320 (NH), 1700 and 1640 (CO); δ_H(270 MHz) 1.60 (1 H, br, NH), 2.36 (2 H, ov, 6-H), 3.25 and 3.35 [each 1 H, each d, *J* 14.0, NHC*H*$_2$furyl(2)], 3.35 and 3.47 (each 3 H, each s, 1- and 3-Me), 4.26 and 4.35 (each 1 H, each d, *J* 13.9, C*H*$_2$Ph), 4.44 (1 H, br, 5-H), 4.75 (1 H, ddd, *J* 4.0, 9.2, and 9.9, 7-H), 5.89 (1 H, ddd, *J* 1.5, 1.8 and 8.9, 8-H) and 6.0–7.3 (total 8 H, Ph and furyl-H); δ_C(67 MHz) 28.6 (1-Me), 32.9 (C-6), 35.5 (3-Me), 44.1 [*C*H$_2$ furyl(2)], 49.6 (*C*H$_2$Ph), 58.2 (C-5), 107.2 and 108.0 (C-7 and -4a), 128.5 (C-8), 110.1, 141.4 and 151.4 (furyl C), 128.7, 128.8, 129.2 and 135.1 (Ph C), 153.2 (C-9a), 153.9 (C-2) and 162.8 (C-4); *m*/*z* 392 (M$^+$).

1,3-*Dimethyl*-2,4-*dioxo*-6-*piperidino*-1,2,3,4-*tetrahydro*-*pyrimidine*-5-*carbaldehyde* **4** was obtained as needles from hexane–benzene; m.p. 133–135 °C (Found: C, 57.5; H, 6.8; N, 16.8. $C_{12}H_{17}N_3O_3$ requires C, 57.35; H, 6.82; N, 16.72%); δ_H(270 MHz) 1.3–1.9 (6 H, ov, CH$_2$), 2.5–3.4 (4 H, ov, CH$_2$), 3.00 and 3.13 (each 3 H, each s, 1- and 3-Me) and 9.45 (1 H, s, CHO).

A solution of substrates **1a** (1.0 mmol), **2a** (1.2 mmol), and two crystals of PTSA in benzene (5 cm^3) was stirred at room temperature for 10 h and the reaction mixture was concentrated to dryness at the same temperature. Its NMR measurement showed it to be 14:72:14 mixture of starting compound **1a**, imine **5a** and pyrimidoazepine **3a**. The benzene solution (5 cm^3) of the reaction mixture was heated under reflux for 8 h. After work-up, a 24:76 mixture of products **3a** and **6a** (0.282 g, 73%) was obtained. Flash chromatography of the mixture on silica gel with hexane–ethyl acetate (5:1) as eluent afforded separate products **3a** and **6a**.

6-(N-Allylbenzylamino)-1,3-dimethyl-5-[(phenylimino)-methyl]pyrimidine-2,4(1*H*,3*H*)-dione **5a**; δ_H(270 MHz) 3.24 and 3.28 (each 3 H, each s, 1- and 3-Me), 3.63 (2 H, d, *J* 6.5 NC*H*$_2$CH=), 4.18 (2 H, s, C*H*$_2$Ph), 5.0 (2 H, ov, =CH$_2$), 5.74 (1 H, m, CH=), 6.4–7.4 (10 H, Ph) and 8.60 (1 H, s, CH=N).

1-*Benzyl*-6,8-*dimethyl*-3-*phenyl*-1,2,3,4-*tetrahydro*-2,4-*ethano*-*pyrimido*[4,5-d]*pyrimidine*-5,7(6H,8H)-*dione* **6a** was obtained as prisms from hexane–benzene; m.p. 161–162 °C (Found: C, 71.2; H, 6.2; N, 14.4. $C_{23}H_{24}N_4O_2$ requires C, 71.11; H, 6.23; N, 14.42%); ν_{max}/cm^{-1} 1685 and 1630 (CO); δ_H(270 MHz) 2.1 and 2.3 (total 4 H, ov, 9- and 10-H$_2$), 3.24 and 3.38 (each 3 H, each s, 6- and 8-Me), 4.15 and 4.27 (each 1 H, each d, *J* 17.2, C*H*$_2$Ph), 4.96 (1 H, d, *J* 3.3, 4-H), 5.14 (1 H, d, *J* 6.6, 2-H) and 6.8–7.5 (10 H, Ph); δ_C(67 MHz) 27.8 (6-Me), 31.6 and 33.5 (C-9 and -10), 35.2 (8-Me), 53.2 (*C*H$_2$Ph), 55.3 (C-4), 75.6 (C-2), 98.4 (C-4a), 117.4, 120.4, 126.4, 129.1, 129.4, 129.8, 135.9 and 145.7 (PhC), 152.6 and 152.7 (C-7 and -8a) and 161.1 (C-5); *m*/*z* 426 (M$^+$) and 335 (M$^+$ − CH$_2$Ph).

5-*Anilino*-9-*benzyl*-1,3,6-*trimethyl*-6,9-*dihydro*-5H-*pyrimido*-[4,5-b]*azepine*-2,4(1H,3H)-*dione* **7a** was obtained as prisms from hexane–benzene; m.p. 208–210 °C (Found: C, 71.8; H, 6.5; N, 14.1. $C_{24}H_{26}N_4O_2$ requires C, 71.62; H, 6.51; N, 13.92%); ν_{max}/cm^{-1} 3390 (NH), 1690 and 1620 (CO); *m*/*z* 402 (M$^+$).

Compound **7a** (major): δ_H(400 MHz) 1.00 (3 H, d, *J* 7.3, 6-Me), 2.75 (1 H, m, 6-H), 3.40 and 3.44 (each 3 H, each s, 1- and 3-Me), 3.49 (1 H, d, *J* 8.8, NH; exchanged with D_2O), 4.28 (2 H, br s, C*H*$_2$Ph), 4.46 (1 H, ddd, *J* 1.5, 2.2 and 9.8, 7-H), 5.10 (1 H, ddd, *J* 1.5, 2.2, and 8.8, 5-H; changed to dd after D_2O treatment, *J* 1.5 and 2.2), 5.90 (1 H, dd, *J* 2.4 and 9.8, 8-H) and

6.3, 6.6 and 7.1–7.3 (total 10 H, Ph); δ_C(100 MHz) 20.9 (6-Me), 28.6 (1-Me), 35.6 (3-Me), 37.4 (C-6), 50.4 (CH_2Ph), 58.2 (C-5), 108.5 (C-7), 112.2 (C-4a), 113.1, 116.4, 127.3, 128.6, 129.1, 129.3, 129.4, 135.1 and 147.3 (C-8 and Ph C), 151.9 (C-9a), 153.0 (C-2) and 162.6 (C-4).

Isomer **7a** (minor): δ_H(400 MHz) 0.97 (3 H, d, *J* 7.3, 6-Me), 2.43 (1 H, m, 6-H), 3.38 (1 H, d, *J* 8.0, NH; exchanged with D_2O), 3.33 and 3.44 (each 3 H, each s, 1- and 3-Me), 4.22 (3 H, ov, 5-H and CH_2Ph), 4.92 (1 H, dd, *J* 1.5 and 7.3, 7-H), 5.90 (1 H, ov, 8-H) and 6.1, 6.5 and 7.1–7.4 (Ph); δ_C(100 MHz) (assigned signals) 15.9, 28.3, 34.2, 36.2, 53.8, 57.4, 103.6, 113.0, 118.9 and 129.7.

9-Benzyl-5-isobutylamino-1,3,6-trimethyl-6,9-dihydro-5H-pyrimido[4,5-b]*azepine-2,4(1H,3H)-dione* **7b** was obtained as plates from hexane; m.p. 122–123 °C (Found: C, 68.9; H, 7.7; N, 14.6. $C_{22}H_{30}N_4O_2$ requires C, 69.08; H, 7.91; N, 14.65%); ν_{max}/cm^{-1} 3300 (NH), 1690 and 1625 (CO); *m/z* 382 (M^+).

Isomer **7b** (major); δ_H(400 MHz) 0.74 and 0.76 (each 3 H, each d, *J* 6.1, $CHMe_2$), 1.08 (3 H, d, *J* 7.3, 6-Me), 1.25 (1 H, m, $CHMe_2$), 1.87 (1 H, dd, *J* 6.6 and 12.2, $NHCH_2CH$), 1.9 (1 H, br, NH; exchanged with D_2O), 1.96 (1 H, dd, *J* 7.2 and 12.2, $NHCH_2CH$), 2.55 (1 H, m, 6-H), 3.37 and 3.48 (each 3 H, each s, 1- 3-Me), 4.22 (1 H, dd, *J* 1.5 and 1.9, 5-H), 4.25 and 4.36 (each 1 H, each d, *J* 14.2, CH_2Ph), 4.45 (1 H, ddd, *J* 1.4, 1.9 and 9.8, 7-H), 5.79 (1 H, dd, *J* 2.4 and 9.8, 8-H) and 7.2 and 7.3–7.4 (total 5 H, Ph); δ_C(100 MHz) 20.5, 20.7 and 21.0 (6-Me and $CHMe_2$), 28.1 and 28.5 (1-Me and $CHMe_2$), 35.3 and 37.1 (C-6 and 3-Me), 55.3 and 55.5 (CH_2Ph and $NHCH_2CH$), 58.1 (C-5), 109.4 (C-7), 113.6 (C-4a), 126.5, 128.6, 128.8, 129.1 and 135.2 (C-8 and Ph C), 150.6 (C-9a), 153.2 (C-2) and 163.0 (C-4).

Isomer **7b** (minor): δ_H(400 MHz) (assigned signals) 0.82 and 0.83 (each 3 H, each d, *J* 6.6, $CHMe_2$), 0.91 (3 H, d, *J* 6.9, 6-Me), 1.53 (1 H, ov, $CHMe_2$), 1.75 (1 H, dd, *J* 5.6 and 11.0, $NHCH_2$), 2.43 (1 H, m, 6-H), 3.26 (1 H, br, d, *J* 2.3, 5-H), 3.33 and 3.44 (each 3 H, each s, 1- and 3-Me), 4.16 (1 H, d, *J* 14.2, CH_2Ph), 4.86 (1 H, dd, *J* 5.6 and 8.2, 7-H), 5.75 (1 H, ov, 8-H) and 7.2–7.5 (5 H, Ph); δ_C(100 MHz) (assigned signals) 16.0, 20.5, 21.0, 28.1, 33.9, 57.0, 57.1, 58.7, 119.3, 128.4, 128.5, 129.0, 129.1, 136.4 and 163.4.

5-Anilino-1-benzyl-1,3-dimethyl-6-phenyl-6,9-dihydro-5H-pyrimido[4,5-b]*azepine-2,4(1H,3H)-dione* **8a** was obtained as plates from ethanol; m.p. 172–174 °C (Found: C, 75.0; H, 6.25; N, 12.1. $C_{29}H_{28}N_4O_2$ requires C, 74.92; H, 6.28; N, 12.06%); ν_{max}/cm^{-1} 3400 (NH), 1700 and 1630 (CO); *m/z* 464 (M^+).

Isomer **8a** (major): δ_H(400 MHz) 3.42 and 3.48 (each 3 H, each s, 1- and 3-Me), 3.67 (1 H, d, *J* 8.3, NH; exchanged with D_2O), 3.93 (1 H, m, 6-H), 4.34 (2 H, s, CH_2Ph), 4.87 (1 H, ddd, *J* 1.5, 2.2 and 10.3, 7-H), 5.37 (1 H, ddd, *J* 1.5, 2.2 and 8.3, 5-H; changed to br after D_2O treatment), 6.15 (1 H, ov, 8-H) and 6.1–6.2, 6.5 and 6.9–7.4 (total 15 H, 3 × Ph); δ_C(100 MHz) 28.7 (1-Me), 35.7 (3-Me), 47.5 (C-6), 51.5 (CH_2Ph), 58.2 (C-5), 108.4 (C-7), 109.7 (C-4a), 113.0, 116.6, 126.7–131.2, 135.0, 142.9 and 146.7 (C-8 and Ph C), 151.8 (C-9a), 153.0 (C-2) and 162.5 (C-4).

Isomer **8a** (minor): δ_H(400 MHz) 3.08 and 3.54 (each 3 H, each s, 1- and 3-Me), 3.75 (1 H, ddd, *J* 1.5, 2.4 and 5.9, 6-H), 4.33 (2 H, s, CH_2Ph), 4.55 (1 H, dd, *J* 2.4 and 10.3, 5-H; changed to d after D_2O treatment, *J* 2.4), 5.04 (1 H, dd, *J* 5.9 and 9.3, 7-H), 6.23 (1 H, dd, *J* 2.4 and 9.3, 8-H) and 6.1–6.2, 6.30, 6.64 and 6.9–7.4 (NH and Ph); δ_C(100 MHz) 28.2 (1-Me), 33.9 (3-Me), 46.3 (C-6), 53.9 (CH_2Ph), 57.7 (C-5), 103.7 (C-7), 113.0 (C-4a), 114.1, 117.0, 126.7–131.2, 136.4, 139.9 and 146.2 (C-8 and Ph C), 149.5 (C-9a), 152.8 (C-2) and 162.4 (C-4).

9-Benzyl-5-isobutylamino-1,3-dimethyl-6-phenyl-6,9-dihydro-5H-pyrimido[4,5-b]*azepine-2,4(1H,3H)-dione* **8b** was obtained as needles from hexane–benzene; m.p. 154–156 °C (Found: C, 72.8; H, 7.2; N, 12.3. $C_{27}H_{32}N_4O_2$ requires C, 72.95; H, 7.26; N, 12.60%); ν_{max}/cm^{-1} 3340 (NH), 1700 and 1625 (CO); *m/z* 444 (M^+).

Isomer **8b** (major): δ_H(400 MHz) 0.46 and 0.53 (each 3 H, each d, *J* 6.8, $CHMe_2$), 1.13 (1 H, m, $CHMe_2$), 1.61 (1 H, br, NH), 1.7–1.9 (2 H, ov, NCH_2CH), 3.40 and 3.53 (each 3 H, each s, 1- and 3-Me), 3.74 (1 H, m, 6-H), 4.34 and 4.48 (each 1 H, each d, *J* 14.7, CH_2Ph), 4.47 (1 H, br, 5-H), 4.84 (1 H, ddd, *J* 1.7, 2.2 and 9.6, 7-H), 6.02 (1 H, dd, *J* 2.4 and 9.6, 8-H) and 7.2–7.4 (10 H, Ph); δ_C(100 MHz) 20.3 and 20.5 ($CHMe_2$), 28.0 (3-Me), 35.2 (1-Me), 28.8 ($CHMe_2$), 47.5 (CH_2Ph), 55.6 (C-6), 56.7 ($NHCH_2CH$), 58.0 (C-5), 109.3 (C-7), 110.9 (C-4a), 126.3–130.9, 135.2 and 144.0 (C-8 and Ph C), 151.4 (C-9a), 153.0 (C-2) and 163.0 (C-4).

Isomer **8b** (minor): δ_H(400 MHz) 0.78 and 0.83 (each 3 H, each d, *J* 6.8, $CHMe_2$), 1.54 (1 H, m, $CHMe_2$), 1.7–1.8 (2 H, ov, NCH_2CH), 2.93 (1 H, br, NH), 3.06 and 3.52 (each 3 H, each s, 1- and 3-Me), 3.44 (1 H, br, 5-H), 3.75 (1 H, ov, 6-H), 4.28 and 4.30 (each 1 H, each d, *J* 5.6, CH_2Ph), 4.98 (1 H, dd, *J* 5.9 and 9.3, 7-H), 6.15 (1 H, dd, *J* 1.8 and 9.3, 8-H) and 7.0–7.4 (10 H, ov, Ph); δ_C(100 MHz) 20.7 and 21.1 ($CHMe_2$), 28.0 (1-Me), 28.6 ($CHMe_2$), 35.2 (3-Me), 50.0 (CH_2Ph), 56.8 (NCH_2CH), 57.4 (C-6), 60.1 (C-5), 109.3 (C-7), 114.7 (C-4a), 126.3–130.9, 136.4 and 144.0 (C-8 and Ph C), 151.4 (C-9a), 153.2 (C-2) and 161.6 (C-4).

Ethyl 5-anilino-9-benzyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,6,9-hexahydro-5H-pyrimido[4,5-b]*azepine-6-carboxylate* **9a** was obtained as needles from hexane–benzene; m.p. 166–168 °C (Found: C, 67.6; H, 6.2; N, 11.8. $C_{26}H_{28}N_4O_4$ requires C, 67.81; H, 6.13; N, 12.17%); ν_{max}/cm^{-1} 3400 (NH), 1730, 1700, 1680 and 1640 (CO).

Isomer **9a** (major): δ_H(270 MHz) 1.02 (3 H, t, *J* 7.3, OCH_2Me), 3.42 and 3.47 (each 3 H, each s, 1- and 3-Me), 3.5 (1 H, ov, NH; exchanged with D_2O), 3.96 (2 H, q, *J* 7.3, OCH_2Me), 4.3 (total 3 H, ov, 6-H and CH_2Ph), 5.09 (1 H, ddd, *J* 1.8, 2.2 and 10.3, 7-H), 5.95 (1 H, ddd, *J* 1.5, 2.2 and 9.3, 5-H; changed to dd after D_2O treatment, *J* 1.5 and 2.2), 6.14 (1 H, dd, *J* 2.4 and 10.3, 8-H) and 6.3, 6.6 and 7.0–7.5 (10 H, Ph); δ_C(67 MHz) 13.9 (CH_2Me), 28.7 (1-Me), 35.9 (3-Me), 47.2 and 47.8 (OCH_2Me and CH_2Ph), 58.4 (C-6), 61.2 (C-5) 103.9 (C-7), 106.7 (C-4a), 113.5, 117.1, 128.9–129.4, 134.9 and 146.3 (C-8 and Ph C), 152.0 and 152.9 (C-2 and -9a), 162.3 (C-4) and 171.1 (CO_2).

Isomer **9a** (minor): δ_H(270 MHz) (assigned signals) 1.22 (CH_2Me), 3.35 and 3.44 (1- and 3-Me), 4.10 (CH_2Me) and 4.93 (7-H); δ_C(67 MHz) (assigned signals) 14.1, 28.3, 34.3, 47.9, 52.5, 57.8, 60.4, 103.2, 108.9, 134.9 and 146.0.

Acknowledgements

Financial support of this work by the Ministry of Education, Science, and Culture of Japan (Grant No. 03650705) is gratefully acknowledged. We also thank Professors M. Tashiro and S. Kanemasa of Kyushu University for measurements of elemental analyses and NMR spectra.

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Paper 3/04950G
Received 16*th August* 1993
Accepted 18*th October* 1993