A FACILE PREPARATION OF FUSED PYRIMIDINE DERIVATIVES *VIA* INTRAMOLECULAR CYCLOADDITION REACTION OF NITRONE[1]

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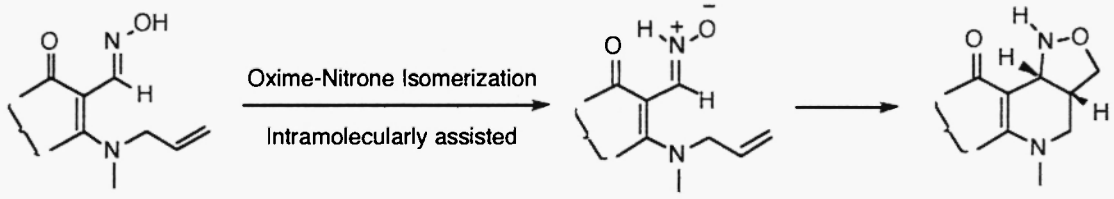
Abstract: The oximes **3** of 6-(alk-2-enyl)amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-carboxaldehydes (**1**) underwent the thermally induced nitrone-cycloaddition reaction leading to isoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidines in good yields, in which the facile oxime-nitrone isomerization would be attributed to the assistance by the intramolecular functionalized groups. This is an alternative route to the isoxazolopyridopyrimidines from the oximes.

Intramolecular 1,3-dipolar cycloaddition reaction on the pyrimidine ring have provided a powerful tool for preparation of novel fused pyrimidine derivatives; pyrazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine *via* nitrile imine-,[2a] and azomethine imine-,[2b] isoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine *via* nitrile oxide-[2c] and *N*-substituted nitrone-cycloaddition reaction.[2c] Recently, we reported the facile oxime-nitrone isomerization at the periphery of pyran,[3a] 1-benzopyran,[3a] pyridine,[3b] and pyrido[1,2-*a*]pyrimidine[3b] systems. Therein, the alkenylamino nitrogen and/or carbonyl group in the oximes would play a role as intramolecular catalyst in the isomerization of oxime to nitrone (Scheme 1). In the course of our study, we examined the oxime-nitrone isomerization aiming for the generation of the *N*-unsubstituted nitrone and its intramolecular cycloaddition reaction at the pyrimidine system.

Scheme 1

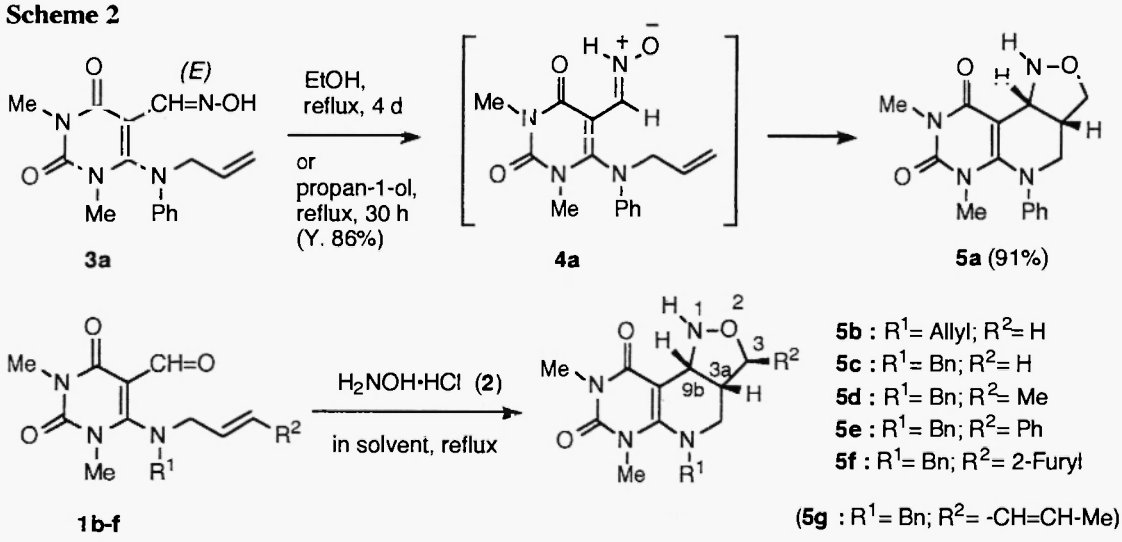


Results and Discussion

6-(*N*-Allylanilino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-carboxaldehyde oxime (**3a**) was obtained similarly to the method reported by Sandhu.[2c] The thermal reaction of oxime **3a** in ethanol (EtOH) for 4 days gave 6,8-dimethyl-5-phenyl-1,3,3a,4,5,9b-hexahydroisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine (**5a**) in 91% yield. This means that the thermal isomerization of oxime **3a** to the *N*-unsubstituted nitrone **4a** followed by its intramolecular cycloaddition affords isoxazolopyridopyrimidine **5a**. The thermally induced nitrone-cycloaddition reaction suggested another access to the isoxazolopyridopyrimidine from oxime **3a** instead of that of the nitrile oxide,[2c] which was generated by the treatment of oxime **3a** with sodium hypochlorite. In order to elucidate the scope and limitations of this method, we examined the reaction of 6-(alk-2-enyl)amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehydes **1** with hydroxylamine hydrochloride (**2**) under several conditions; the reaction of **1** with **2** in EtOH under reflux followed by neutralization with 5% aqueous sodium hydrogen carbonate (Method A) or the similar reaction in the presence of triethylamine (Method B) provided **5b-f**

in fair to good results (Scheme 2 and Table 1). The reaction of 6-(3-substituted prop-2-enyl)amino substrates **1d-f** with **2** gave the corresponding cycloadducts **5d-f** as single diastereomers. The structural confirmation of the fused pyrimidines **5** was accomplished on the basis of their analytical and spectral data. The stereochemistry of the resulting isoxazolidine ring in **5** were deduced to be 3,3a-*trans* (*J*= 3.2 - 3.4 Hz for **5d-f**) and 3a,9b-*cis* (*J*= 6.8 - 7.1 Hz) from the coupling constants in comparison with those of the related systems.[2,4] The isoxazolidine ring formation proceeded with the retention of alkenyl configuration as expected. Our next concern was focused on the oxime-nitrone isomerization in this system. Oximes **3b-g** could be isolated in pure forms by the modified Sandhu's method; the reaction of **1c** with **2** in the presence of sodium acetate in methanol at 0°C for 1 h gave the oxime **3c** in 68% yield (Scheme 3). The thermal reaction of the isolated oximes **3b-g** in solvents gave the desired cycloadducts **5b-g** in good to excellent yields (Scheme 3). While the features of the similar

Scheme 2



Method A: 1) **2**, EtOH, reflux; 2) 5% aq. $NaHCO_3$; 3) extracted with CH_2Cl_2; 4) SiO_2 column separation
Method B: 1) **2**, Et_3N, EtOH (benzene), reflux; 2) extracted with CH_2Cl_2; 3) SiO_2 column separation

Table 1. Preparation of Isoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidines **5** by the Reaction of Aldehydes **1** with Hydroxylamine Hydrochloride (**2**).

Entry	R^1	R^2	Solvent	Method	Time/h	Product (Yield/%)[a]
1	Allyl	H	EtOH	A	6	**5b** (92)
2	Allyl	H	benzene	B	30	**5b** (89)
3	Bn	H	EtOH	A	12	**5c** (84)
4	Bn	H	benzene	B	36	**5c** (70)
5	Bn	Me	EtOH	B	28	**5d** (74)
6	Bn	Ph	EtOH	A	20	**5e** (88)
7	Bn	2-Furyl	EtOH	A	6	**5f** (98)

[a] Based on isolated products.

Scheme 3

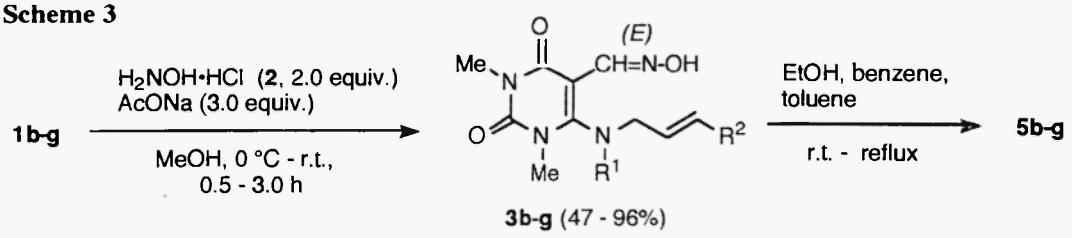


Table 2. Thermal Conversion of Oximes **3** to Isoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidines **5**.

Entry	Oxime	R^1	R^2	Solvent	Temp./°C	Time/h	PTSA (equiv.)	Product (Yield/%)[a]
1	**3b**	Allyl	H	EtOH	reflux	36	none	**5b** (quant.)
2	**3c**	Bn	H	EtOH	reflux	48	none	**5c** (82)
3	**3c**	Bn	H	toluene	reflux	40	none	**5c** (65) [78][b]
4	**3d**	Bn	Me	EtOH	reflux	24	none	**5d** (86)
5	**3d**	Bn	Me	benzene	reflux	42	none	**5d** (76) [86][b]
6	**3e**	Bn	Ph	EtOH	reflux	20	none	**5e** (92)
7	**3e**	Bn	Ph	benzene	reflux	24	none	**5e** (92)
8	**3e**	Bn	Ph	EtOH	reflux	3	1.0	**5e** (85)
9	**3f**	Bn	2-Furyl	EtOH	reflux	3	none	**5f** (quant.)
10	**3f**	Bn	2-Furyl	EtOH	25	3	1.0	**5f** (quant.)
11	**3g**	Bn	-CH=CH-Me	EtOH	reflux	15	none	**5g** (87)

[a] Based on isolated products. [b] Yield based on the consumed oxime.

oxime-nitrone isomerization in our other systems slightly depended on the solvents utilized.[2] the reaction of **3** in EtOH and benzene proceeded cleanly to give only **4** along with a small amount of polymeric materials. The rates of isomerization and cycloaddition reaction of oximes **3** except for **3f** were considerably slower than those of the other oximes previously reported.[2] In some cases, oximes **3c-e** could be recrystallized from EtOH. As shown in Table 1, the Method A was superior to the Method B in order to complete the reaction in a limited period of time. This suggested the effects of the acidic conditions on the reaction rate. In contrast to the results for the 1-benzopyran oximes,[3a] the addition of toluene-*p*-sulfonic acid (PTSA) to the solution of **3e,f** caused a significant acceleration of the reaction rates (Table 2, Entries 8 and 10). However, an apparent improvement of the yields could not be accomplished.

In conclusion, we have described that a facile oxime-nitrone isomerization takes place at the periphery of pyrimidine system and the intramolecular cycloaddition reaction of the resulting *N*-unsubstituted nitrone intermdiates provides a fruitful route to isoxazolopyridopyrimidine derivatives. Further investigations to elucidate the synthetic utility of the oxime-nitrone isomerization are under progress in our laboratory.

Experimental

For general details of apparatuses and procedures, see the previous paper.[3a] ^1H and ^{13}C NMR spectra were measured on JEOL EX-270 spectrometer (at 270 MHz for ^1H and 68 MHz for ^{13}C) in deuteriochloroform solution, unless otherwise stated. Overlapping splitting patterns in ^1H NMR spectra are indicated as ov.

Oximes. Oxime **3a** was a known compound; mp 180-182 °C (lit.[2c] mp 180-182 °C); ^1H NMR δ= 3.22, 3.43 (1- and 3-Me), 4.19 (>NCH$_2$-), 5.30, 5.34 (=C*H*$_2$), 5.95 (-CH=), 6.69-7.31 (Ph), 7.85 (-CH=N-), 10.17 (OH). Oximes **3b-g** were obtained from aldehydes **1b-g**, hydroxylamine hydrochloride (**2**; 2.0 equiv.), sodium acetate (3.0 equiv.) in methanol at 0 °C to room temperature for 0.5-1.0 h in 47-96% yields. Their structures were fully assigned on basis of their analytical and spectral data, the selected data of which were shown as follows: **Oxime 3b**: mp 133-134 °C; ^1H NMR δ= 3.37, 3.42 (1- and 3-Me), 3.69 (>NCH$_2$-), 5.24 (=C*H*$_2$), 5.73 (-CH=), 7.97 (-CH=N-), 9.72 (OH). **Oxime 3c:** mp 140-141 °C; ^1H NMR δ= 3.34, 3.37 (1- and 3-Me), 3.59 (>NCH$_2$-), 4.21 (C*H*$_2$Ph), 5.27, 5.32 (=C*H*$_2$), 6.31 (-CH=), 7.15-7.39 (Ph), 7.84 (-CH=N-), 10.06 (OH). **Oxime 3d:** mp 119-121 °C; ^1H NMR δ= 1.75 (=CH-*Me*), 3.33, 3.37 (1- and 3-Me), 3.52 (>NCH$_2$-), 4.21 (C*H*$_2$Ph), 5.44, 5.70 (-C*H*=C*H*-), 7.14-7.38 (Ph), 7.82 (-CH=N-), 10.18 (OH). **Oxime 3e:** mp 100-102 °C; ^1H NMR δ=3.37, 3.40 (1- and 3-Me), 3.75 (>NCH$_2$-), 4.24 (C*H*$_2$Ph), 6.15, 6.54 (-C*H*=C*H*-), 7.18-7.41 (Ph), 7.92 (-CH=N-), 9.48 (OH). **Oxime 3f:** mp 77-78 °C; ^1H NMR δ= 3.35, 3.36 (1- and 3-Me), 3.71 (>CH$_2$-), 4.22 (C*H*$_2$Ph), 6.03-6.38 (-C*H*=C*H*- and Furyl-H), 7.15-7.35 (Ph and Furyl-H and OH), 7.85 (-CH=N-). **Oxime 3g:** mp 78-80 °C; ^1H NMR δ= 1.79 (=CH-*Me*), 3.34, 3.37 (1- and 3-Me), 3.59 (>NCH$_2$-), 4.21 (C*H*$_2$Ph), 5.45-6.16 (-C*H*=C*H*-C*H*=C*H*-), 7.15-7.37 (Ph), 7.83 (-CH=N-), 10.18 (OH).

Preparation of Isoxazolo[3',4':4,5]pyrido[2,3-d]pyrimidines 5. General Procedures: A solution of aldehyde **1c** (0.626 g, 2.0 mmol) and hydroxylamine hydrochloride (**2**; 0.167 g, 2.40 mmol) in EtOH (10 ml) was heated under reflux for 40 h. The EtOH was evaporated to dryness, which was extracted with dichloromethane (30 ml x 3). The organic layer was dried over anhydrous magnessium sulfate and the dichloromethane was evaporated. The residue was subjected to column chromatography on silica gel to afford cycloadduct **5c** (0.551 g, 84%) with hexane/ethyl acetate (1/3).

Cycloadduct 5a: colorless crystals; mp 157-159 °C; IR cm^{-1}: 3250 (NH), 1690, 1630 (CO); ^1H NMR δ= 2.68 (1 H, m, 3a-H), 2.96, 3.39 (each 3 H, each s, 6- and 8-Me), 3.51-3.59 (2 H, ov, 3- and 4-H), 3.75 (1 H, dd, *Jgem*= 13.6, *J3a,4*= 4.6 Hz, 4-H), 4.04 (1 H, dd, *Jgem*= 8.3, *J3,3a*= 7.6 Hz, 3-H), 4.36 (1 H, *J3a,9b*= 7.5 Hz, 9b-H), 7.03-7.40 (6 H, ov, NH and Ph); ^{13}C NMR δ= 28.1, 32.5 (6- and 8-Me), 37.9 (3a-C), 53.9, 54.4 (3a- and 9b-C), 71.2 (3-C), 97.8 (9a-C), 122.9, 125.2, 130.2, 145.6 (Ph-C), 151.1 (5a-C), 152.1 (7-C), 163.1 (9-C). Anal. Found: C, 61.05; H, 5.91; N, 17.66%. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.83%.

Cycloadduct 5b: yellow oil; IR (neat) cm^{-1}: 3250 (NH), 1690, 1640 (CO); ^1H NMR δ= 2.65 (1 H, m, 3a-H), 2.94 (1 H, dd, *Jgem*= 13.9, *J3a,4*= 11.9 Hz, 4-H), 3.24 (1 H, dd, *Jgem*= 13.9, *J3a,4*= 5.0 Hz, 4-H), 3.33, 3.38 (each 3 H, each s, 6- and 8-Me), 3.46-3.69 (4 H, ov, 3-H and >NCH$_2$- and NH), 4.14-4.21 (2 H, ov, 3-

and 9b-H), 5.35-5.44 (2 H, ov, =C*H*$_2$), 5.88 (1 H, m, -CH=); ^{13}C NMR δ= 27.7, 32.9 (6- and 8-Me), 35.0 (3a-C), 47.1 (4-C), 54.2, 54.3 (9b-C and >NCH$_2$-), 71.3 (3-C), 94.9 (9a-C), 118.8 (=CH$_2$), 131.9 (-CH=), 151.1 (5a-C), 154.5 (7-C), 162.9 (9-C). Anal. Found: C, 56.56; H, 6.30; N, 19.98%. Calcd for $C_{13}H_{18}N_4O_3$: C, 56.10; H, 6.52; N, 20.13%.

Cycloadduct 5c: colorless prisms (hexane-benzene); mp 132-134 °C; IR cm^{-1}: 3200 (NH), 1690, 1630 (CO); ^{1}H NMR δ= 2.41 (1 H, m, 3a-H), 3.01 (1 H, t, *Jgem*= 13.8, *J3a,4*= 13.8 Hz, 4-H), 3.16 (1 H, dd, *Jgem*= 13.8, *J3a,4*= 5.3 Hz, 4-H), 3.36, 3.43 (each 3 H, each s, 6- and 8-Me), 3.49 (1 H, dd, *Jgem*= 8.6, *J3,3a*= 2.3 Hz, 3-H), 4.06 (1 H, dd, *Jgem*= 8.6, *J3,3a*= 7.2 Hz, 3-H), 4.13 (1 H, d, *J3a,9b*= 6.9 Hz, 9b-H), 4.12, 4.20 (each 1 H, each d, *Jgem*= 18.8 Hz, C*H*$_2$Ph), 4.73 (1 H, br, NH), 7.27-7.44 (5 H, ov, Ph); ^{13}C NMR δ= 27.9, 33.1 (6- and 8-Me), 35.1 (3a-C), 47.8 (4-C), 54.1 (9b-C), 55.4 (*C*H$_2$Ph), 71.5 (3-C), 95.9 (9a-C), 127.1, 128.1, 129.1, 135.3 (Ph-C), 152.3 (5a-C), 154.4 (7-C), 163.1 (9-C); MS *m/z* 328 (M$^+$). Anal. Found: C, 61.78; H, 6.20; N, 16.70%. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06%.

Cycloadduct 5d: colorless plates (hexane-benzene); mp 164-165 °C; IR cm^{-1}: 3200 (NH), 1690, 1630 (CO); ^{1}H NMR δ= 1.27 (3 H, d, *J3,Me*= 6.2 Hz, 3-Me), 1.93 (1 H, m, 3a-H), 3.03 (1 H, dd, *Jgem*= 13.9, *J3a,4*= 12.8 Hz, 4-H), 3.17 (1 H, dd, *Jgem*= 13.9, *J3a,4*= 5.1 Hz, 4-H), 3.36, 3.42 (each 3H, each s, 6- and 8-Me), 3.71 (1 H, qd, *J3,Me*= 6.2, *J3,3a*= 3.3 Hz, 3-H), 4.11, 4.26 (each 1 H, each d, *Jgem*= 16.1 Hz, C*H*$_2$Ph), 4.18 (1 H, d, *J3a,9b*= 6.9 Hz, 9b-H), 7.28-7.46 (6 H, ov, NH and Ph); ^{13}C NMR δ= 19.2 (3-Me), 27.9, 33.1 (6- and 8-Me), 41.4 (3a-C), 47.4 (4-C), 54.1 (9b-C), 55.3 (*C*H$_2$Ph), 78.5 (3-C), 95.0 (9a-C), 126.9, 128.2, 129.1, 135.2 (Ph-C), 152.3 (5a-C), 154.6 (7-C), 163.1 (9-C); MS *m/z* 342 (M$^+$). Anal. Found: C, 63.24; H, 6.46; N, 16.26%. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36%.

Cycloadduct 5e: colorless plates (EtOH); mp 194-195 °C; IR cm^{-1}: 3210 (NH), 1690, 1630 (CO): ^{1}H NMR δ= 2.33 (1 H, m, 3a-H), 3.18-3.30 (2 H, ov, 4-H), 3.38, 3.42 (each 3H, each s, 6- and 8-Me), 4.08, 4.24 (each 1 H, each d, *Jgem*= 16.1 Hz, C*H*$_2$Ph), 4.33 (1 H, d, *J3a,9b*= 6.8 Hz, 9b-H), 4.55 (1 H, d, *J3,3a*= 3.4 Hz, 3-H), 5.35 (1 H, br, NH), 7.26-7.42 (10 H, ov, Ph); ^{13}C NMR δ= 28.0, 33.2 (6- and 8-Me), 43.0 (3a-C), 47.8 (4-C), 54.6 (9b-C), 55.3 (*C*H$_2$Ph), 84.2 (3-C), 95.1 (9a-C), 126.2, 126.9, 128.1 x 2, 128.6, 129.1, 135.2, 139.6 (Ph-C), 152.0 (5a-C), 154.7 (7-C), 163.1 (9-C); MS *m/z* 404 (M$^+$). Anal. Found: C, 68.44; H, 6.05; N, 13.91%. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85%.

Cycloadduct 5f: colorless plates (EtOH); mp 105-106 °C; IR cm^{-1}: 3200 (NH), 1700, 1640 (CO); ^{1}H NMR δ= 2.62 (1 H, m, 3a-H), 3.12-3.34 (2 H, ov, 4-H), 3.37, 3.43 (each 3 H, each s, 6- and 8-Me), 4.13, 4.27 (each 1 H, each d, *Jgem*= 16.2 Hz, C*H*$_2$Ph), 4.22 (1 H, br, NH), 4.46 (1 H, d, *J3a,9b*= 6.9 Hz, 9b-H), 4.63 (1 H, d, *J3,3a*= 2.3 Hz, 3-H), 6.28, 6.34 (each 1 H, Furyl-H), 7.27-7.42 (6 H, ov, Ph and Furyl-H); ^{13}C NMR δ= 28.5, 33.5 (6- and 8-Me), 40.1 (3a-C), 47.9 (4-C), 54.9, 55.8 (9b-C and *C*H$_2$Ph), 78.1 (3-C), 109.2, 110.9, 129.2, 143.5 (Furyl-C), 127.4, 128.6, 129.6, 135.7 (Ph-C), 151.9 (9a-C), 152.8 (5a-C), 154.8 (7-C), 163.6 (9-C). Anal. Found: C, 64.12; H, 5.80; N, 14.01%. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.21%.

Cycloadduct 5g: colorless prisms (hexane-benzene), mp 105-106 °C; IR cm^{-1}: 3250 (NH), 1690, 1630 (CO); ^1H NMR δ= 1.69 (3 H, dd, *JCH-Me*= 6.3, *Jallylic*= 1.3 Hz, =CH-*Me*), 3.36, 3.41 (each 3 H, each s, 6- and 8-Me), 3.98 (1 H, dd, *Jgem*= 7.3, *J3,3a*= 3.0 Hz, 3-H), 4.11, 4.26 (each 1 H, each d, *Jgem*= 16.5 Hz, CH_2Ph), 4.21 (1 H, d, *J3a,9b*= 6.9 Hz, 9b-H), 5.44-5.75 (2 H, ov, C*H*=C*H*), 6.1-7.0 (1 H, br, NH), 7.32-7.46 (5 H, ov, Ph); ^{13}C NMR δ= 17.8 (=CH-*Me*), 28.0, 33.2 (6- and 8-Me), 40.7 (3a-C), 47.5 (4-C), 54.4 (9b-C), 55.3 (CH_2Ph), 77.2 (3-C), 95.5 (9a-C), 126.9, 128.1, 129.2, 135.4 (Ph-C), 128.4, 130.5 (*C*H=*C*H), 152.4 (5a-C), 154.6 (7-C), 163.2 (9-C). Anal. Found: C, 65.98; ZH, 6.62; N, 15.00%. Calcd for $C_{20}H_{24}N_4O_3$: C, 66.30; H, 6.36; N, 14.73%.

References and Notes

(1) Studies on Fused Pyrimidine Derivatives. Part 16. Part 15 in this series: Kobayashi, T.; Ikuno, K.; Noguchi, M.; Kakehi, A. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1453.

(2) a) Noguchi, M.; Nagata, S.; Kajigaeshi, S. *Chem. Pharm. Bull.* **1984**, *34*, 3994; b) Noguchi, M.; Yamada, K. *Synthesis* **1993**, 145; c) Prajapati, D.; Bhuyan, P.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 607.

(3) a) Gotoh, M.; Mizui, T.; Sun, B.; Hirayama, K.; Noguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1857; b) Gotoh, M.; Sun, B.; Hirayama, K.; Noguchi, M. *Tetrahedron* **1996**, *52*, 887.

(4) The stereochemistry of the fused isoxazolidine ring resulted from intramolecular nitrone-cycloaddition reaction was elaborately examined using the coupling constants; Oppolzer, W.; Keller, K. *Tetrahedron Lett.* **1970**, 117; Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 226; Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277; Hassner,m A.; Maurya, R.; Friedman, O.; Gottlieb, H. E.; Padwa, A.; Austin, D. *J. Org. Chem.* **1993**, *58*, 4539; Hassner, A.; Falb, E.; Nudelman, A.; Albeck, A.; Gottlieb, H. E. *Tetrahedron Lett.* **1994**, *35*, 2397. Also, see the references cited therein.

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