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Intramolecular 1,3-Dipolar Cycloaddition at the Periphery of Heterocyclic Systems. Part 3.[1] A Facile Hydrazone-Azomethine Imine Isomerization at the Periphery of Pyridine and Pyrido[1,2-*a*]pyrimidine Systems

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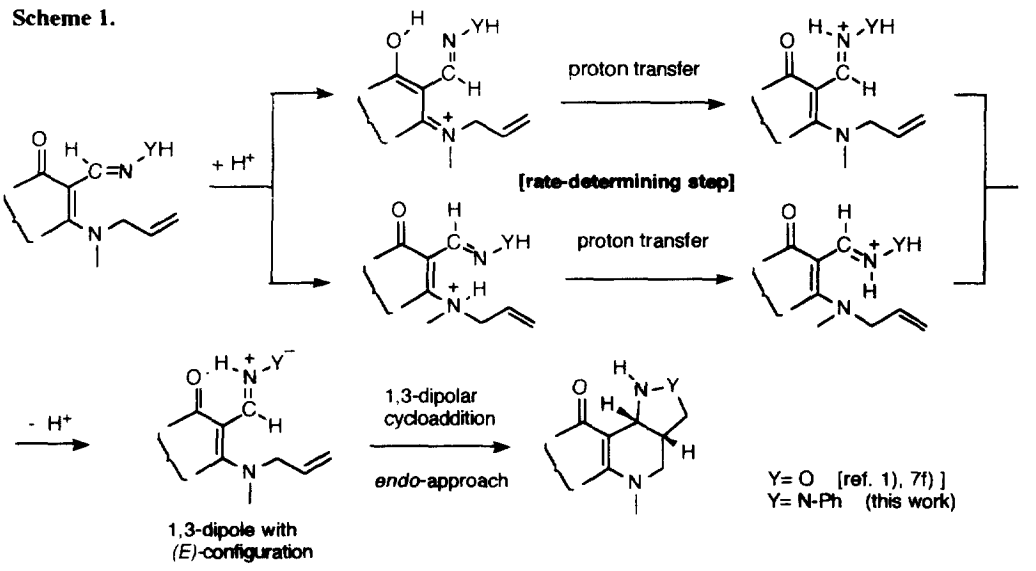
Abstract: The phenylhydrazones of 2-(alk-2-enylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes and 4-(alk-2-enylamino)-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehydes underwent the thermally induced 1,3-dipolar cycloaddition leading to a mixture of the fused pyrazolidine and pyrazoline derivatives under extremely mild conditions. For the observed facile hydrazone-azomethine imine isomerization, we proposed an intramolecularlly assisted process similar to that for the facile oxime-nitrone isomerization in these systems; the intramolecular proton transfer from the the protonated alkenylamino and/or carbonyl moieties to the imine nitrogen facilitated the generation of the azomethine imine intermediates.

Introduction

In the preceding paper, we reported a facile oxime-nitrone isomerization and successive intramolecular nitrone cycloaddition reaction at the periphery of pyridine and pyrido[1,2-*a*]pyrimidine systems;[1] 2-(alk-2-eylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oximes underwent the thermally induced 1,3-dipolar cycloaddition reaction giving the fused isoxazolidine derivatives. We proposed, therein, that the intramolecular proton transfer from the protonated alkenylamino and/or carbonyl moieties to the oxime nitrogen should be attributed to the facile generation of the nitrone intermediate (Scheme 1). These results demonstrated

Scheme 1.

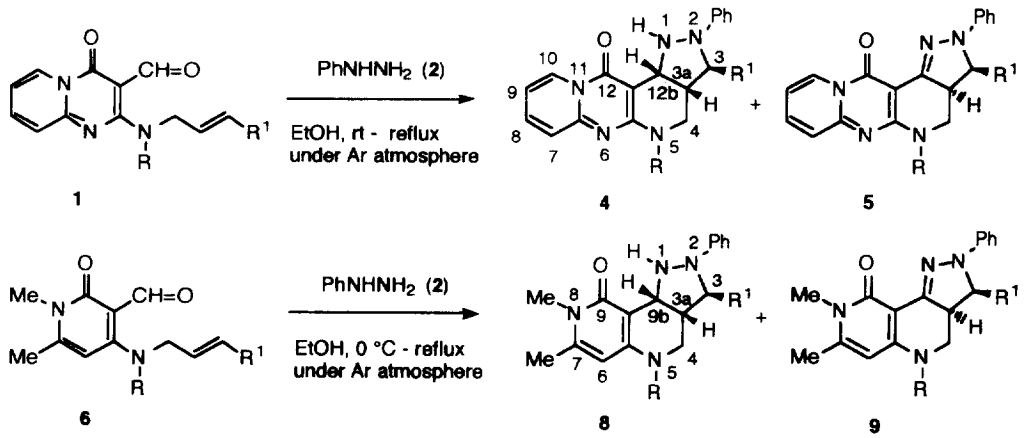


that pyridine and pyrido[1,2-*a*]pyrimidine systems seemed to be good ones for elucidating the new concept of 1,3-dipole generation through the formal 1,2-proton transfer proposed by Grigg.[2] Our attention was focused on the investigations of the thermal isomerization of imines and hydrazones to their 1,3-dipolar tautomers in these systems. The imines of the aldehydes did not undergo the thermally induced 1,3-dipolar cycloaddition but the thermal imine-ene reaction giving the fused azepine derivatives, in which the imine moieties played a role as enophile.[3] The concept of the thermal hydrazone-azomethine imine isomerization was proposed in 1978[4a] earlier than that of oxime-nitrone one.[2] However, further investigations[4] on the synthetic and mechanistic aspects have not been accomplished sufficiently in comparison with those on the acid-catalyzed hydrazone-azomethine imine isomerization,[5,6] or on the thermal oxime-nitrone one.[7] As a reason, the resulting pyrazolidine ring was not so stable and dehydrogenated easily to 2-pyrazoline one under the reaction conditions and/or the purification procedures. This provided an ambiguity of the mechanism and stereochemistry of the 1,3-dipolar cycloaddition process. In the course of our studies on the intramolecular 1,3-dipolar cycloaddition at the periphery of heterocyclic systems, we examined the hyrazone-azomethine imine isomerization in these systems under neutral and acidic conditions. The hydrazones were thermally isomerized to the azomethine imine intermediates through the proton transfers by an intramolecular assistance. Further discussions on the isomerization process will be done on the basis of the thermal behaviors of the isolated hydrazones and the kinetic studies on their isomerization.

The Hydrazone-Azomethine Imine Isomerization at the Periphery of Pyridine and Pyrido[1,2-*a*]pyrimidine Systems

The reaction of 2-(*N*-allylbenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1a**) with phenylhydrazine (**2**; 1.1 equiv.) in ethanol (EtOH) at room temperature for 24 h under argon atmosphere gave an inseparable 47:53 mixture of pyrazolidine **4a** and pyrazoline **5a** in 97% total yield. The expected hydrazone **3a** was not detected by ^{1}H NMR spectrum of the reaction mixture. Pyrazolidine **4a** was not so stable and converted to pyrazoline **5a** gradually on standing or heating its EtOH solution under open air. Attempts to separate the products **4a** and **5a** each other by chromatography on silica gel failed; pyrazolidine **4a** was dehydrogenated to **5a** quantitatively. The similar reaction in EtOH under reflux for 9 h gave only pyrazoline **5a** in 83% yield. The structural confirmation of these products **4a** and **5a** was accomplished on the basis of their spectral data in comparison to those of the related systems reported.[4] Similarly, 2-(*N*,*N*-diallylamino)- (**1b**), 2-[*N*-benzyl-(*trans*-but-2-enyl)amino]- (**1c**), and 2-[*N*-benzyl(*trans*-cinnamyl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1d**) were allowed to react with hydrazine **2** to give pyrazolidines **4** and/or pyrazolines **5** depending on the reaction conditions. The reaction of 4-(*N*-allylbenzylamino)- (**6a**), 4-(*N*,*N*-diallylamino)- (**6b**), 4-[*N*-

Scheme 2.



benzyl(*trans*-but-2-enyl)amino]- (**6c**), and 4-[*N*-benzyl(*trans*-cinnamyl)amino]-1,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde (**6d**) with hydrazine **2** gave also pyrazolidines **8** and/or pyrazolines **9** (Scheme 2 and Table 1). In the latter cases, the hydrazones **7** formed initially were not detected.

Table 1. The Reaction of Aldehydes **1** and **6** with Phenylhydrazine (**2**) in EtOH Giving Pyrazolidines **4** and **8** and Pyrazolines **5** and **9**.

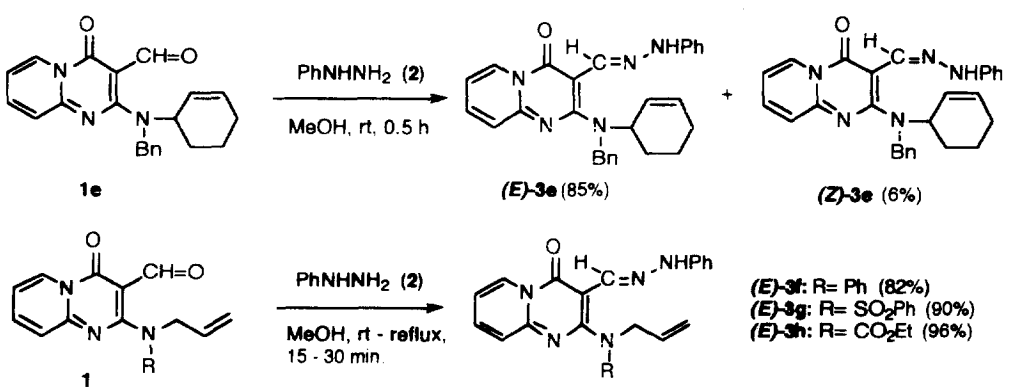
Entry	Aldehyde	R	R^1	Temp/°C	Time/h	Products[a]/%	
1[b]	**1a**	Bn	H	rt	24	**4a**/46	**5a**/51
2[c]	**1a**	Bn	H	reflux	9	**5a**/83	
3[b]	**1b**	$CH_2CH=CH_2$	H	rt	14	**4b**/50	**5b**/32
4[c]	**1c**	Bn	Me	reflux	12	**5c**/80	
5	**1d**	Bn	Ph	rt	6	**4d**/76	**5d**/22
6[c]	**6a**	Bn	H	reflux	2.5	**9a**/91	
7	**6b**	$CH_2CH=CH_2$	H	0	1.5	**8b**/57	**9b**/27
8[b]	**6b**	$CH_2CH=CH_2$	H	reflux	3	**9b**/97	
9	**6c**	Bn	Me	rt	5	**9c**/52[d]	
10[c]	**6c**	Bn	Me	reflux	5	**9c**/59[d]	
11[c]	**6d**	Bn	Ph	reflux	9	**9d**/81	

[a] Isolated yields. [b] The ratios of the products (**4** vs **5**) were determined by ^1H NMR spectra of the crude products. [c] Under open air. [d] Partially decomposed with a column chromatography on silica gel.

Only the pyrazolidines **4d** and **8b** could be isolated in a pure form and the structural confirmation of its *cis*-fused pyrazolidine was accomplished also by the ^1H NMR analysis (J= 5.3-5.9 Hz). Pyrazoline **5c,d** and **8c,d** were obtained as single diastereomers and the stereochemistry between the 3-H and 3a-H was tentatively assigned to be *cis* on the basis of the signal patterns of the ring protons similarly to those of pyrazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine.[4d] These results indicate that the hydrazone-azomethine imine isomerization takes place at the periphery of the pyridine and pyrido[1,2-*a*]pyrimidine systems under milder conditions than the corresponding oxime-nitrone one.

In order to obtain further information on the isomerization, we examined to isolate the hyrazones and investigated their behaviors under thermal and acidic conditions. Attempts to isolate the phenylhydrazones of the above aldehydes in pure forms were made without success; the reaction of aldehyde **1a** with hydrazine **2** in

Scheme 3.



methanol (MeOH) at ≤ 0°C gave a mixture of the desired hydrazone **3a**, pyrazolidine **4a**, and pyrazoline **5a**, in which the hydrazone **3a** was converted to **4a** and **5a** during further purification procedures. Interestingly, the reaction of 2-[*N*-benzyl(cyclohex-2-en-1-yl)amino]-4-exo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1e**) with hydrazine **2** in MeOH at room temperature for 0.5 h gave a mixture of the hydrazones ***(E)*-** and ***(Z)*-3e**, both of which could be isolated each other by crystallization and column chromatography on silica gel. The phenylhydrazones **3f-h** with *E*-configuration were obtained by the reaction of 2-(*N*-allylanilino)- (**1f**), 2-[*N*-allyl(benzenesulfonyl)amino]- (**1g**), and 2-[*N*-allyl(ethoxycarbonyl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1h**) with hydrazine **2**, respectively (Scheme 3)

Heating of hydrazone ***(E)*-3e** in EtOH under reflux for 4 h afforded pyrazoline **5e** in 86% yield. Hydrazone ***(Z)*-3e** also underwent the thermally induced 1,3-dipolar cycloaddition giving the pyrazoline **5e** in 73% yield, in which a significant decrease in the rate of the conversion was observed (in refluxing EtOH for 48 h). The thermal behaviors of the isolated hydrazones **3f-h** were also examined; a prolonged reaction time or an elevated reaction temperature was required for the conversion of hydrazones **3f,g** to pyrazolines **5f,g**. While hydrazone **3h** was unchanged on heating in EtOH, its heating in butan-1-ol caused a decomposition of the hydrazone **3h** (Scheme 4). These results are summarized in Table 2.

Scheme 4.

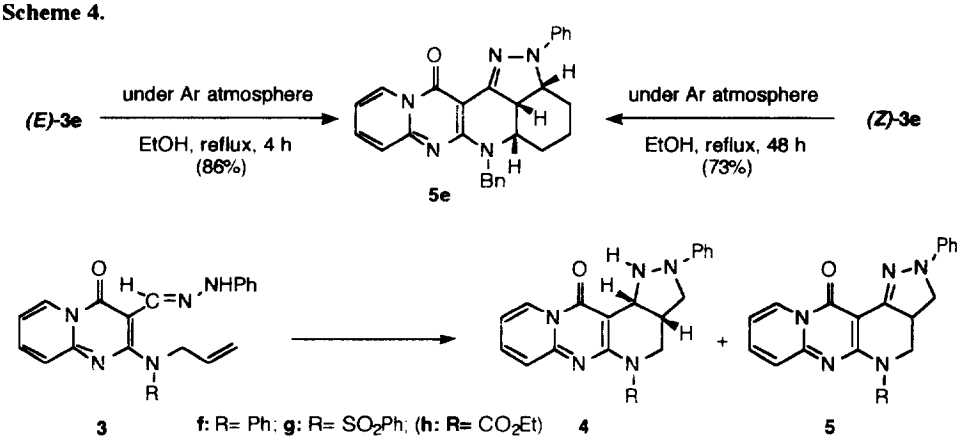


Table 2. The Thermal Behaviors of the Isolated Hydrazones **3f-h** in Refluxing Solvents under Argon Atmosphere.

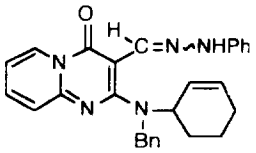
Entry	Hydrazone	R	Solvent	Time/h	Product[a]/% (Ratio of **4** vs **5**)[b]	Recovered Hydrazone[b]/%
1	**3f**	Ph	EtOH	18	**4f, 5f** (86:14)/90	
2	**3f**	Ph	dioxane	15	**5f**/65	**3f**/18
3	**3g**	SO_2Ph	EtOH	72	**4g, 5g** (23:77)/52	
4	**3g**	SO_2Ph	toluene	45	**5g**/54	
5[c]	**3g**	SO_2Ph	dioxane	2	**4g, 5g** (23:77)/66	
6	**3g**	SO_2Ph	butan-1-ol	9	**5g**/78	
7	**3h**	CO_2Et	EtOH	24	no reaction	**3h**/86
8	**3h**	CO_2Et	butan-1-ol	6	d	

[a] Isolated yield. [b] Determined by ^1H NMR spectra of the crude products. [c] PTSA (2.0 equiv.) was added to the reaction mixture. [d] Many products owing to the decomposition of hydrazone **3h** were obtained.

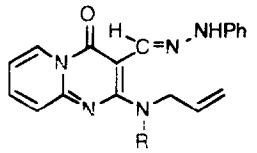
In the preceding paper,[1] we reported that the oxime of aldehyde **6a** with *E*-configuration was more reactive in the isomerization to the nitrone than the counterpart *(Z)*-isomer and that the basicity of the alkenylamino nitrogen in the oximes affected the facility of the isomerization. These results suggested that the oxime-nitrone and hydrazone-azomethine imine isomerizations in these systems had the similar mechanistic features; the generation of 1,3-dipoles through the proton transfer by an intramolecular assistance. More details on these isomerization processes will be discussed in the next section.

A Mechanistic Proposal for the Hydrazone-Azomethine Imine Isomerization at the Periphery of Pyrido[1,2-*a*]pyrimidine System

Our next concern was focused on the kinetics of the hydrazone-azomethine imine isomerization. The rates of the conversion of hydrazones ***(E)*-3e** (R= Bn); **3f** (R= Ph), and **3g** (R= SO_2Ph) in dioxane and butan-1-ol using a HPLC method (see the Experimental section). The conversion rates of the hydrazones were first-order with respect to their concentrations. The rate constants for hydrazone ***(E)*-3e** in dioxane at 50.7 °C were independent of its initial concentrations; 0.900 x 10^{-4} s^{-1} at 6.67 x 10^{-4} M and 1.11 x 10^{-4} s^{-1} at 6.67 x 10^{-3} M (Table 3, Entries 1 and 2).



***(E)*-3e**
***(Z)*-3e**



***(E)*-3f**: R= Ph
***(E)*-3g**: R= SO_2Ph

Table 3. Relative Rates and Activation Parameters for the Conversion of Hydrazones ***(E)*-3e** and ***(Z)*-3e**.

Entry	Hydrazone	Solvent	Temp/°C	Additive (equiv.)	Relative Rate
1	***(E)*-3e**	dioxane	50.7	-	1.00
2[a]	***(E)*-3e**	dioxane	50.7	-	1.23
3	***(E)*-3e**	dioxane	50.7	Et_3N (2.0)	1.12
4	***(E)*-3e**	butan-1-ol	50.7	-	4.30
5	***(E)*-3e**	dioxane	50.7	PTSA (0.2)	1700
6	***(E)*-3e**	dioxane	50.7	PTSA (2.0)	b
7	***(Z)*-3e**	dioxane	78.3	-	1.00
8	***(Z)*-3e**	dioxane	78.3	PTSA (2.0)	78.0

			Activation Parameters[c]		
			$\Delta G^{\neq}$(kcal mol^{-1})	$\Delta H^{\neq}$(kcal mol^{-1})	$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})
9	***(E)*-3e**	dioxane	24.48	23.92	- 1.89
10	***(Z)*-3e**	dioxane	27.39	19.18	- 27.53

[a] Carried out in ten-fold concentration. [b] Too fast to measure the rate. [c] At the standard state (25.0 °C).

For the conversion of hydrazones ***(E)*-** and ***(Z)*-3e**, the relative rates under several conditions and the activation parameters are summarized in Table 3. The behaviors of the *(E)*- and *(Z)*-isomers under acidic conditions were of particular interest. In contrast to the reaction of the oxime in 1-benzopyran system,[7f] the addition of toluene-*p*-sulfonic acid (PTSA) to the dioxane solution of the hydrazones ***(E)*-** and ***(Z)*-3e** accelerated both the rates and it was more effective for the hydrazone **3e** with *E*-configuration than that with *Z*-

configuration. The effects of solvent and PTSA on the conversion rates of hydrazone **3g** (R= SO_2Ph) and their activation parameters are summarized in Table 4. In comparison to the results of the oximes in 1-benzopyran[7f] and pyrido[1,2-*a*]pyrimidine[1] systems, the nature of solvent and the acidic conditions affected the conversion rates. It should be noted that too large negative value of the activation entropy and, in contrast, small value of the activation enthalpy for the conversion of hydrazone **3g** in dioxane suggested a concerted process *via* the 1,2-hydrogen shift of the hydrazone. The rate for the conversion of **3g** in butan-1-ol at 97.2 °C was faster by 4.6 times than that in dioxane and the features of its activation parameters were considerablly different from those in dioxane. A change from the concerted process to an intramolecularly assisted one in the reaction mechanism was suggested. The relative rates of hydrazones **3e**, **3f**, and **3g** in dioxane at 68.8 °C are also demonstrated in Table 4, in which the conversion rate of hydrazones is facilitated as the basicity of the alkenylamino moieties increases.

Table 4. Relative Rates for the Conversion of Hydrazones ***(E)*-3e**, ***(Z)*-3e**, **3f**, and **3g** and Activation Parameters for that of **3g**.

Entry	Hydrazone	Solvent	Temp./°C	Additive (equiv.)	Relative Rate
1	***(E)*-3e**	dioxane	68.8	-	13.6
2[a]	***(Z)*-3e**	dioxane	68.8	-	0.75
3	**3f**	dioxane	68.8	-	3.12
4[a]	**3g**	dioxane	68.8	-	1.00
5	**3g**	dioxane	97.2	-	1.00
6	**3g**	DMF	97.2	-	1.66
7	**3g**	butan-1-ol	97.2	-	4.63
8	**3g**	dioxane	97.2	PTSA (2.0)	11.8

			Activation Parameters[b]		
			$\Delta G^{\neq}$ (kcal mol^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal K^{-1} mol^{-1})
9	**3g**	dioxane	26.10	10.53	- 52.23
10	**3g**	butan-1-ol	26.95	19.45	- 25.16

[a] Extrapolated value. [b] At the standard state (25.0 °C).

These mean that the mechanistic features for the facile oxime-nitrone isomerization (Scheme 1; Y= O)[1] could be available for the facile hydrazone-azomethine imine one (Scheme 1; Y= NPh); the hydrazone is protonated intermolecularly onto the alkenylamino and/or carbonyl moieties. The proton was transferred intramolecularly to the lone pair of the imino nitrogen giving an iminium product, which release the proton of the hydrazone giving the *N*-protonated (or *N*-unsubstituted) azomethine imine intermediate. The proton transfer step seems to be the rate-determining one of the generation of the nitron intermediate. The inspections using molecular models revealed that only the hydrazones with *E*-configuration were possible to transfer the proton intramolecularly from the protonated alkenylamino and/or carbonyl moieties to the imine lone pair in the hydrazones. Therefore, the *E*/*Z*-configuration of the hydrazones as well as the oximes should affect their conversion rates; the conversion rate of ***(E)*-3e** in dioxane at 68.8 °C was faster by 18.3 times than that of *(Z)*-isomer (Table 4, Entries 1 and 2).

Conclusion

As mentioned above, while the oxime with *Z*-configuration in the pyridine system did not undergo the thermally induced 1,3-dipolar cycloaddition on heating in EtOH, the *E*-counterpart was easily converted to the cycloadduct under the same conditions.[1] On the other hand, both *E*- and *Z*-isomers of hydrazone **3e** underwent the cycloaddition on heating in EtOH. Some different behaviors under acidic conditions between the hydrazones

and oximes were also found. While the addition of the proton source into the system did not effect significantly in the conversion rates of the oximes, it caused a remarkable enhancement in the rates of the hydrazones.

Although the exact reasons for these observed differences are still obscure, plausible explanations can be given as bellows; 1) It is well known that oximes have a unique place in the azomethine chemistry because of their resistance to thermal (non-catalytic) *E/Z*-isomerization.[8] The *E/Z*-isomerization of oximes is normally achieved either photochemically[9] or in the presence of strong acids.[10] 2) From the kinetic data for the thermal *E/Z*-isomerization of ordinary hydrazones,[11] the $\Delta G^{\neq}$ for the isomerization could be estimated to be 20-25 kcal mol^{-1} in our systems. The *E/Z*-isomerization of hydrazones was facilitated by utilizing a trace of protic acid, reaching an equilibrium even at room temperature.[12] These suggests that the hydrazone-azomethine imine isomerization in this work would be competitive with the *E/Z*-isomerization of hydrazones *via* thermal and/or acid-catalyzed processes in some cases. The significant enhancement of the conversion rate of hydrazone **3e** in *acidic* media (Table 3, Entries 5 and 6) would suggest a change of reaction mechanism. However, the [3^+ + 2] cycloaddition reaction of hydrazones *via* cationic dipoles[6] seemed to require more strongly acidic conditions.[5] We have no evidence on the exact reaction mechanism of the conversion of hydrazones to pyrazolines in *acidic* media.

In two successive papers, we have described the thermal isomerization of the oximes and hydrazones to their 1,3-dipolar tautomers in pyridine and pyrido[1,2-*a*]pyrimidine systems in *neutral* media. The structural features of the oximes and hydrazones cause the facile generation of the 1,3-dipoles by an intramolecular assistance in the proton transfer. The most plausible structures for the resulting nitrone and azomethine imine intermediates are demonstrated in Scheme 1, in which the hydrogen bond between NH in the *N*-protonated 1,3-dipoles and carbonyl oxygen would provide a stabilization of the 1,3-dipoles. It is expected that the stabilization by the hydrogen bond inclines the oxime-nitrone and hydrazone-azomethine imine equilibrium to the 1,3-dipolar tautomers. We suggest that it is the second cause for the facile isomerization of the oximes and hydrazones to their 1,3-dipolar tautomers in these systems. Further investigations on the latter cause, on the reaction scope, and on the extensions of this concept to the synthetic tools are in progress in our laboratory.

Experimental

For general details of apparatuses and procedures, see the previous paper.[7f] ^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.

Aldehydes. Aldehyds **1** and **6** as the starting materials were known compounds.[1,3]

Reaction of Aldehydes 1 with Phenylhydrazine (2); Typical Procedures: A solution of aldehyde **1a** (0.160 g, 0.50 mmol) in EtOH (15 ml) was deoxygenated by introducing argon for 1 h. Phenylhydrazine (**2**; 0.059 ml, 0.55 mmol) was added the solution and the mixture was stirred at room temperature for 24 h under argon atmosphere. The solvent was evaporated and the residue was crystallized with hexane (15 ml) containing a few drops of EtOH to give a mixture of pyrazolidine **4a** and pyrazoline **5a** (0.197 g, 97%; **4a**:**5a**= 47:53). Similarly, the solution of **1a** and **2** in EtOH was heated under reflux for 9 h under open air. Evaporation and crystallization with EtOH gave pyrazoline **5a** (83%).

(3a*S**,12b*R**)-5-Benzyl-12-oxo-2-phenyl-1,2,3,3a,4,5,12,12b-octahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidine (**4a**): this compound was obtained as yellow crystals. However, the analytical sample for **4a** coulld not be accomplished because of its instability. The structure of **4a** was deduced to be the *cis*-fused pyrazolidine by ^1H NMR spectrum of the mixture of **4a** and **5a**. ^1H NMR δ= 2.61 (1 H, m, 3a-H), 3.15-3.76 (4 H, ov, 3- and 4-H), 4.41 (1 H, d, *J*= 5.3 Hz, 12b-H), 4.94, 5.12 (each 1 H, each d, *J*= 15.2 Hz,

CH_2Ph), 6.75-7.36 (12 H, ov, 7-, 9-H and Ph), 7.59 (1 H, m, 8-H), 8.96 (1 H, d, *J*= 6.9 Hz, 10-H), NH, not detected.

5-Benzyl-12-oxo-2-phenyl-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidine (**5a**): yellow needles from ethyl acetate (AcOEt); mp 209-211 °C; IR (KBr) 1670 cm^{-1} (CO); ^{1}H NMR δ= 3.23 (1 H, dd, *J*= 9.6, 11.9 Hz, 3-H), 3.44 (1 H, dd, *J*= 13.5, 13.9 Hz, 4-H), 3.63-3.79 (2 H, ov, 3a- and 4-H), 4.09 (1 H, dd, *J*= 9.6, 9.9 Hz, 3-H), 4.94, 5.12 (each 1 H, each d, *J*= 15.2 Hz, CH_2Ph), 6.80 (1 H, dd, *J*= 6.6, 6.9 Hz, 9-H), 7.11-7.38 (11 H, ov, 7-H and Ph), 7.59 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 9.02 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 42.2 (3a-C), 50.0 (4-C), 51.7, 51.7 (*C*H_2Ph and 3-C), 87.4 (12a-C), 113.2 (9-C), 113.2, 118.6, 127.5, 127.6, 128.6, 128.7, 137.4, 145.7 (Ph-C), 124.3 (7-C), 128.0 (10-C), 136.6 (8-C), 146.4 (12b-C), 149.8 (6a-C), 152.9 (5a-C), 157.8 (12-C). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.20; N, 17.19%. Found: C, 73.91; H, 5.38; N, 17.26%.

(3a*S**,12b*R**)-5-Allyl-12-oxo-2-phenyl-1,2,3,3a,4,5,12,12b-octahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidine (**4b**): this compound was obtained as red crystals. However, the analytical sample for **4b** coulld not be accomplished because of its instability. The structure of **4b** was deduced to be the *cis*-fused pyrazolidine by ^{1}H NMR spectrum of the mixture of **4b** and **5b**. ^{1}H NMR δ= 2.65 (1 H, m, 3a-H), 3.18-3.75 (4 H, ov, 3- and 4-H), 4.26-4.55 (3 H, ov, 12b- and C*H*$_2$CH=CH$_2$), 5.19-5.27 (2 H, ov, CH$_2$CH=C*H*$_2$), 5.87 (1 H, m, CH$_2$C*H*=CH$_2$), 6.76-7.29 (7 H, ov, 7-, 9-H and Ph), 7.58 (1 H, m, 8-H), 8.94 (1 H, d, *J*= 6.9 Hz, 10-H), NH, not detected.

5-Allyl-12-oxo-2-phenyl-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]-pyrimidine (**5b**): red needles from EtOH; mp 205-207 °C; IR (KBr) 1680 cm^{-1} (CO); ^{1}H NMR δ= 3.23 (1 H, dd, *J*= 9.6, 11.9 Hz, 3-H), 3.47 (1 H, t, *J*=13.5 Hz, 4-H), 3.65-3.80 (2 H, ov, 3a- and 4-H), 4.10 (1 H, t, *J*= 9.6 Hz, 3-H), 4.28, 4.44 (each 1 H, each d, *J*= 5.6, 15.5 Hz, C*H*$_2$CH=CH$_2$), 5.23 (1 H, dd, *J*= 1.3, 10.9 Hz, CH$_2$CH=C*H*$_2$), 5.24 (1 H, dd, *J*= 1.3, 16.2 Hz, CH$_2$CH=C*H*$_2$), 5.84 (1 H, m, CH$_2$C*H*=CH$_2$), 6.80-7.27 (7 H, ov, 7-, 9-H and Ph), 7.56 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 8.98 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 42.3 (3a-C), 50.0 (4-C), 51.2 (*C*H$_2$CH=CH$_2$), 51.8 (3-C), 87.6 (12a-C), 113.2 (9-C), 113.3, 118.7, 128.8, 145.9 (Ph-C), 117.4 (CH$_2$CH=*C*H$_2$), 124.3 (7-C), 128.0 (10-C), 133.3 (CH$_2$*C*H=CH$_2$), 136.8 (8-C), 146.5 (12b-C), 149.8 (6a-C), 152.9 (5a-C), 157.6 (12-C). Anal. Calcd for $C_{21}H_{19}N_5O$: C, 70.57; H, 5.36; N, 19.60%. Found: C, 70.58; H, 5.21; N, 19.48%.

(3*S**,3a*R**)-5-Benzyl-3-methyl-12-oxo-2-phenyl-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido-[2,3-*d*]pyrido[1,2-*a*] pyrimidine (**5c**): yellow needles from benzene-AcOEt; mp 212-214 °C; IR (KBr): 1680 cm^{-1} (CO); ^{1}H NMR δ= 1.53 (3 H, d, *J*= 5.9 Hz, 3-Me), 3.24 (1 H, ddd, *J*= 5.9, 9.9, 12.5 Hz, 3a-H), 3.39 (1 H, dd, *J*=11.2, 12.5 Hz, 4-H), 3.62 (1 H, dd, *J*= 5.9, 11.2 Hz, 4-H), 3.81 (1 H, dq, *J*= 9.9, 5.9 Hz, 3-H), 4.94, 5.14 (each 1 H, each d, *J*= 15.2 Hz, C*H*$_2$Ph), 6.82-7.61 (12 H, ov, 7-, 9-H and Ph), 7.58 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 9.02 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 20.4 (3-Me), 50.0 (4-C), 50.8 (3a-C), 51.8 (*C*H$_2$Ph), 60.0 (3-C), 87.3 (12a-C), 113.1 (9-C), 114.8, 119.5, 127.4, 127.5, 128.6, 128.6, 137.3, 144.6 (Ph-C), 124.3 (7-C), 128.0 (10-C), 136.6 (8-C), 146.3 (12b-C), 149.8 (6a-C), 153.0 (5a-C), 157.5 (12-C). Anal. Calcd for $C_{26}H_{23}N_5O$: C, 74.09; H, 5.50; N, 16.62%. Found: C, 73.93; H, 5.55; N, 16.43%.

(3*R**,3a*S**,12b*R**)-5-Benzyl-2,3-diphenyl-12-oxo-1,2,3,3a,4,5,12,12b-octohydropyrazolo[3,'4':4,5]-pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidine (**4d**): pale yellow crystals without recrystallizazion; mp 177-178 °C; IR (KBr) 3220 (NH), 1680 cm^{-1} (CO); ^{1}H NMR δ= 2.53 (1 H, m, 3a-H), 3.26 (1 H, dd, *J*= 9.0, 12.6 Hz, 4-H), 3.43 (1 H, dd, *J*= 5.0, 12.6 Hz, 4-H), 4.27 (1 H, d, *J*= 3.3 Hz, 3-H), 4.4-4.9 (1 H, br, NH, exchangable with D$_2$O), 4.81, 5.12 (each 1 H, each d, *J*= 15.2 Hz, C*H*$_2$Ph), 4.91 (1 H, d, *J*= 5.9 Hz, 12b-H), 6.65-7.35 (17 H, ov, 7-, 9-H and Ph), 7.55 (1 H, m, 8-H), 8.94 (1 H, d, *J*= 6.6 Hz, 10-H); ^{13}C NMR δ= 45.8 (4-C), 47.6 (3a-

C), 51.1 (*C*H$_2$Ph), 52.4 (12b-C), 70.0 (3-C), 89.1 (12a-C), 112.5 (9-C), 113.2, 118.0, 125.9, 127.3, 127.5, 128.1, 128.5, 128.7, 128.8, 137.9, 143.0, 149.8 (Ph-C), 124.3 (7-C), 127.6 (10-C), 136.3 (8-C), 150.4 (6a-C), 157.7 (5a-C), 157.7 (12-C). Anal. Calcd for $C_{31}H_{27}N_5O$: C, 76.67; H, 5.60; N, 14.42%. Found: C, 75.99; H, 5.65; N, 13.93%.

(3*R**,3a*S**)-5-Benzyl-2,3-diphenyl-12-oxo-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]-pyrido[1,2-*a*] pyrimidine (**5d**): yellow needles from EtOH; mp 224-226 °C; IR (KBr) 1680 cm^{-1} (CO); ^{1}H NMR δ= 3.50 (1 H, m, 3a-H), 3.56-3.65 (2 H, ov, 4-H), 4.62 (1 H, d, *J*= 10.2 Hz, 3-H), 4.66, 5.31 (each 1 H, each d, *J*= 15.5 Hz, C*H*$_2$Ph), 6.77-7.40 (17 H, ov, 7-, 9-H and Ph), 7.56 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 9.03 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 50.0 (4-C), 52.2 (*C*H$_2$Ph), 53.6 (3a-C), 70.2 (3-C), 87.1 (12a-C), 113.3 (9-C), 114.7, 119.5, 126.1, 127.5, 127.6, 127.8, 128.5, 128.7, 129.3, 137.2 142.0, 144.5 (Ph-C), 124.4 (7-C), 128.1 (10-C), 136.9 (8-C), 146.7(12b-C), 150.0 (6a-C), 153.2 (5a-C), 157.8 (12-C). Anal. Calcd for $C_{31}H_{25}N_5O$: C, 77.00; H, 5.21; N, 14.48%. Found: C, 76.87; H, 5.25; N, 14.30%.

Reaction of Aldehydes 6 with Phenylhydrazine (2); Typical Procedures: A solution of **6b** (0.246 g, 1.0 mmol) in EtOH (6 ml) was deoxygenated by introducing argon for 0.5 h and phenylhydrazine (**2**; 0.108 ml, 1.1 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 1.5 h under argon atmosphere. The solvent was evaporated and the residue was crystallized with hexane-EtOH to give pyrazolidine **8b** (0.192 g, 57%). The filtrate was evaporated and the residue was subjected to column chromatography on silica gel to give a mixture of many products except for the pyrazoline **9b**. Similarly, the solution of **6b** (0.123 g, 0.50 mmol) and phenylhydrazine (**2**; 0.059 ml, 0.55 mmol) in EtOH (3 ml) was heated under reflux for 3 h under open air. The solvent was evaporated and the residue was subjected to column chromatography on silica gel to give pyrazoline **9b** (0.164 g, 98%) with hexane-AcOEt (1:5).

(3a*S**,9b*R**)-5-Allyl-7,8-dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydoro-1*H*-pyrazolo[3,4-*d*]pyrido[4,3-*b*]-pyridin-9(8*H*)-one (**8b**): pale yellow crystals without recrystallizazion; mp 215-217 °C; IR (KBr) 3240 (NH), 1630 cm^{-1} (CO); ^{1}H NMR δ= 1.5–2.1 (1 H, br, NH), 2.28 (3 H, s, 7-Me), 2.56 (1 H, m, 3a-H), 3.11-3.14 (2 H, ov, 4-H), 3.31 (1 H, dd, *J*= 1.3, 9.9 Hz, 3-H), 3.49 (3 H, s, N-Me), 3.67 (1 H, dd, *J*= 6.9, 9.9 Hz, 3-H), 3.87, 4.00 (each 1 H, each dd, *J*= 4.6, 17.5 Hz, C*H*$_2$CH=CH$_2$), 4.22 (1 H, d, *J*= 5.3 Hz, 9b-H), 5.14 (1 H, dd, *J*= 1.7, 17.2 Hz, CH$_2$CH=CH*H*), 5.20 (1 H, dd, *J*= 1.7, 10.2 Hz, CH$_2$CH=C*H*H), 5.68 (1 H, s, 6-H), 5.80 (1 H, m, CH$_2$C*H*=CH$_2$), 6.77-7.26 (5 H, ov, Ph); ^{13}C NMR δ= 21.8 (7-Me), 30.8 (N-Me), 36.9 (3a-C), 48.6 (*C*H$_2$CH=CH$_2$), 53.3 (9b-C), 53.5 (3-C), 56.9 (4-C), 95.8 (6-C), 58.4 (9a-C), 114.5, 118.7, 129.1, 145.5 (Ph-C), 117.3 (CH$_2$CH=*C*H$_2$), 132.8 (CH$_2$CH=CH$_2$), 152.1 (5a-C), 152.8 (7-C), 164.1 (9-C). Anal. Calcd for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.66%. Found: C, 71.40; H, 7.14; N, 16.66%.

5-Allyl-7,8-dimethyl-2-phenyl-3,3a,4,5-tetrahydoro-2*H*-pyrazolo[3,4-*d*]pyrido[4,3-*b*]pyridin-9(8*H*)-one (**9b**): yellow needles from AcOEt; mp 218-220°C; IR (KBr) 1640 cm^{-1} (CO); ^{1}H NMR δ= 2.28 (3 H, s, 7-Me), 3.19 (1 H, dd, *J*= 9.2, 11.9 Hz, 3-H), 3.43-3.70 (3 H, ov, 3a- and 4-H), 3.52 (3 H, s, N-Me), 3.84, 3.98 (each 1 H, each dd, *J*= 4.0, 17.5 Hz, C*H*$_2$CH=CH$_2$), 4.05 (1 H, dd, *J*= 9.2, 9.9 Hz, 3-H), 5.18 (2 H, dd, *J*= 1.0, 10.2, 18.5 Hz, CH$_2$CH=C*H*$_2$), 5.59 (1 H, s, 6-H), 5.80 (1 H, m, CH$_2$C*H*=CH$_2$), 6.77-7.27 (5 H, ov, Ph); ^{13}C NMR δ= 21.7 (7-Me), 30.3 (N-Me), 42.8 (3a-C), 51.4 (*C*H$_2$CH=CH$_2$), 52.9 (3-C), 53.7 (4-C), 95.3 (6-C), 95.9 (9a-C), 113.2, 118.5, 128.7, 146.1 (Ph-C), 118.2 (CH$_2$CH=*C*H$_2$), 131.8 (CH$_2$*C*H=CH$_2$), 146.2 (5a-C), 146.7 (9b-C), 152.1 (7-C), 159.5 (9-C). Anal. Calcd for $C_{20}H_{24}N_4O$: C, 71.83; H, 6.63; N,16.76%. Found: C, 71.72; H, 6.62; N,16.62%.

5-Benzyl-7,8-dimethyl-2-phenyl-3,3a,4,5-tetrahydoro-2*H*-pyrazolo[3,4-*d*]pyrido[4,3-*b*]pyridin-9(8*H*)-one (**9a**): yellow prisms from EtOH; mp 249-250 °C; IR (KBr) 1640 cm^{-1} (CO); ^{1}H NMR δ= 2.22 (3 H, s, 7-Me), 3.16 (1 H, dd, *J*= 9.6, 11.6 Hz, 3-H), 3.47 (3 H, s, N-Me), 3.51-3.72 (3 H, ov, 3a- and 4-H), 4.02 (1 H, *J*=

9.6, 9.9 Hz, 3-H), 4.52 (2 H, s, C*H*$_2$Ph), 5.52 (1 H, s, 6-H), 6.73-7.39 (10 H, ov, Ph); ^{13}C NMR δ= 21.7 (7-Me), 30.3 (N-Me), 42.7 (3a-C), 51.4 (3-C), 53.2 (4-C), 54.7 (*C*H$_2$Ph), 95.3 (6-C), 96.0 (9a-C), 113.3, 118.2, 126.3, 127.6, 128.6, 128.9, 136.6, 146.0(Ph-C), 146.4 (5a-C), 146.6 (9b-C), 152.4 (7-C), 159.5 (9-C). Anal. Calcd for $C_{24}H_{24}N_4O$: C, 71.97; H, 6.29; N, 14.57%. Found: C, 71.99; H, 6.18; N, 14.49%.

(3*S**,3a*R**)-5-Benzyl-3,7,8-trimethyl-2-phenyl-3,3a,4,5-tetrahydoro-2*H*-pyrazolo[3,4-*d*]pyrido[4,3-*b*]-pyridin-9-(8*H*)-one (**9c**): yellow prisms from AcOEt-EtOH; mp 236-238 °C; IR (KBr) 1640 cm^{-1} (CO); ^{1}H NMR δ= 1.52 (3 H, d, J= 9.5 Hz, 3-Me), 2.24 (3 H, s, 7-Me), 3.25 (1 H, m, 3a-H), 3.45-3.57 (2 H, ov, 4-H), 3.49 (3 H, s, N-Me), 3.78 (1 H, m, 3-H), 4.51, 4.63 (each 1 H, each d, C*H*$_2$Ph), 5.64 (1 H, s, 6-H), 6.79-7.40 (10 H, ov, Ph); ^{13}C NMR δ= 20.6 (3-Me), 21.7 (7-Me), 30.3 (N-Me), 51.1 (*C*H$_2$Ph), 53.2 (3a-C), 54.8 (4-C), 59.3 (3-C), 96.2 (6-C), 95.9 (9a-C), 114.6, 119.0, 126.2, 127.6, 128.6, 128.9, 136.5 144.9 (Ph-C), 146.3 (5a-C), 146.5 (9b-C), 152.0 (7-C), 159.6 (9-C). Anal. Calcd for $C_{25}H_{26}N_4O$: C, 75.35; H, 6.58; N, 14.06%. Found: C, 75.21; H, 6.70; N; 13.96%.

(3*R**,3a*R**)-5-Benzyl-7,8-dimethyl-2,3-phenyl-3,3a,4,5-tetrahydoro-2*H*-pyrazolo[3,4-*d*]pyrido[4,3-*b*]-pyridin-9-(8*H*)-one (**9d**): yellow needles from hexane-AcOEt; mp 232-233 °C; IR (KBr): 1640 cm^{-1} (CO); ^{1}H NMR δ= 2.23 (3 H, s, 7-Me), 3.50 (3 H, s, N-Me), 3.47-3.76 (3 H, ov, 3a- and 4-H), 4.40, 4.66 (each 1 H, each d, J= 17.2 Hz, C*H*$_2$Ph), 4.02 (1 H, d, J= 10.9 Hz, 3-H), 5.61 (1 H, s, 6-H), 6.73-7.42 (15 H, ov, Ph); ^{13}C NMR δ= 21.7 (7-Me), 30.4 (N-Me), 53.0 (3a-C), 54.2 (4-C), 55.0 (*C*H$_2$Ph), 69.9 (3-C), 95.4 (6-C), 95.7 (9a-C), 114.6, 119.1, 126.1, 126.1, 127.6, 127.7, 128.4, 129.0, 129.3, 136.2, 142.4, 144.7 (Ph-C), 146.6 (5a-C), 146.9 (9b-C), 152.4 (7-C), 159.7 (9-C). Anal. Calcd for $C_{30}H_{28}N_4O$: C, 78.23; H, 6.13; N, 12.17%. Found: C, 78.02; H, 6.28; N, 12.30%.

Isolation of Phenylhydrazones 3e-h by the Reaction of Aldehyde 1e-h with Hydrazine 2; Typical Procedures: The deoxygenated solution of aldehyde **1e** (0.719 g, 2.0 mmol) and phenylhydrazine (**2**; 0.236 ml, 2.4 mmol) in MeOH (15 ml) was stirred at room temperature for 0.5 h. The solvent was evaporated and the residue was crystallized with diethyl ether (20 ml) to give ***(E)*-3e** (0.761 g, 85%). The MeOH filtrate was evaporated and the residue was subjected to column chromatography on silica gel to give ***(Z)*-3e** (0.055 g, 6%) with hexane-AcOEt (3:1).

2-[*N*-Benzyl(cyclohex-2-en-1-yl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (*E*)-phenylhydrazone [***(E)*-3e**] yellow crystals without recrystallization; mp 160-162 °C; IR (KBr) 3240 (NH), 1650 cm^{-1} (CO); ^{1}H NMR δ= 1.59-2.17 (6 H, ov, CH$_2$), 4.78 (2 H, s, C*H*$_2$Ph), 5.43 (1 H, m, NCH<), 5.80, 5.93 (each 1 H, each m, C*H*=C*H*), 6.80-7.28 (12 H, ov, 7-, 9-H and Ph), 7.50 (1 H, dd, J= 6.6, 8.9 Hz, 8-H), 7.61 (1 H, br s, NH, exchangable with D$_2$O), 7.81 (1 H, s, CH=N), 8.77 (1 H, d, J= 6.9 Hz, 6-H); ^{13}C NMR δ= 21.7, 24.7, 27.9 (CH$_2$), 47.9 (*C*H$_2$Ph), 57.6 (NCH<), 94.3 (3-C), 112.5, 119.3, 126.5, 126.7, 129.1, 129.2, 138.8, 145.2 (Ph-C), 112.7 (7-C), 124.7 (9-C), 127.3 (6-C), 128.2, 131.7 (CH=CH), 134.8 (CH=N), 135.6 (8-C), 147.6 (9a-C), 158.4 (2-C), 158.8 (4-C). Anal. Calcd for $C_{24}H_{21}N_5O$: C, 74.81; H, 6.05; N, 15.58%. Found: C, 75.31; H, 6.21; N, 15.61%.

2-[*N*-Benzyl(cyclohex-2-en-1-yl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (*Z*)-phenylhydrazone [***(Z)*-3e**]: yellow needles from hexane-benzene; mp 123-125 °C; IR (KBr) NH: not detected, 1650 cm^{-1} (CO); ^{1}H NMR δ= 1.60-2.17 (6 H, ov, CH$_2$), 4.58, 4.79 (each 1 H, each d, J= 15.5 Hz, C*H*$_2$Ph), 4.75 (1 H, m, NCH<), 5.62, 5.90 (each 1 H, each m, CH=CH), 6.80-7.36 (13 H, ov, 7-, 9-H, CH=N and Ph), 7.60 (1 H, dd, J= 6.6, 8.9 Hz, 8-H), 8.83 (1 H, br s, NH, exchangable with D$_2$O), 8.93 (1 H, d, J= 6.9 Hz, 6-H); ^{13}C NMR δ= 21.7, 24.6, 28.5 (CH$_2$), 47.6 (*C*H$_2$Ph), 59.6 (NCH<), 93.9 (3-C), 113.4, 119.7, 126.7, 127.6, 128.9, 129.0, 139.8, 146.1 (Ph-C), 113.8 (7-C), 124.8 (9-C), 127.7 (6-C), 128.3, 132.0 (*C*H=*C*H),

132.4 (CH=N), 136.7 (8-C), 148.6 (9a-C), 156.8 (2-C), 162.2 (4-C). Anal. Calcd for $C_{24}H_{21}N_5O$: C, 74.81; H, 6.05; N, 15.58%. Found: C, 74.79; H, 6.07; N, 15.66%.

Similar reaction of aldehyde **1f** with hydrazine **2** in MeOH at room temperature for 0.5 h and the solvent was evaporated. The residue was crystallized with cold EtOH to give ***(E)*-3f** (82%) and the filtrate was evaporated to dryness, which was subjected to column chromatography on silica gel to give ***(Z)*-3f** (2%). The structural assignment on the hydrazones was accomplished by their ^{1}H NMR spectral data.

2-(*N*-Allylanilino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-phenylhydrazone [***(E)*-3f**]: pale red crystals without recrystallization; mp 153-155 °C; IR (KBr) 3260 (NH), 1680 cm^{-1} (CO); ^{1}H NMR δ= 4.81 (1 H, d, *J*= 5.0 Hz, C*H*$_2$CH=CH$_2$), 5.17 (1 H, dd, *J*= 1.7, 10.2 Hz, CH$_2$CH=CH*H*), 5.41 (1 H, dd, *J*= 1.7, 17.2 Hz, CH$_2$CH=C*H*H), 6.09 (1 H, ddt, *J*= 5.0, 10.2, 17.2 Hz, CH$_2$C*H*=CH$_2$), 6.74-7.21 (12 H, ov, 7-H, CH=N and Ph), 7.41 (1 H, br s, NH, exchangable with D$_2$O), 7.42 (1 H, d, *J*= 8.9 Hz, 9-H), 7.63 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 8.95 (1 H, d, *J*= 6.9 Hz, 6-H); ^{13}C NMR δ= 54.7 (*C*H$_2$CH=CH$_2$), 95.5 (3-C), 112.5, 119.0, 123.9, 124.5, 128.7, 128.8, 144.7, 146.2 (Ph-C), 113.5 (7-C), 116.5 (CH$_2$CH=*C*H$_2$), 124.9 (9-C), 127.4 (6-C), 133.0 (CH=N), 134.9 (CH$_2$*C*H=CH$_2$), 136.1 (8-C), 148.5 (9a-C), 158.0 (2-C), 158.5 (4-C). Anal. Calcd for $C_{24}H_{21}N_5O$: C, 72.89; H, 5.35; N, 17.71%. Found: C, 73.05; H, 5.54; N, 17.94%.

(Z)-Isomer [***(Z)*-3f**]: red crystals without recrystallization; mp 133-134 °C; IR (KBr) NH, not detected, 1640 cm^{-1} (CO); ^{1}H NMR δ= 4.71 (2 H, d, *J*= 5.6 Hz, C*H*$_2$CH=CH$_2$), 5.15 (1 H, d, *J*= 8.9 Hz, =CH*H*), 5.19 (1 H, d, *J*= 16.8 Hz, =C*H*H), 6.06 (1 H, m, -C*H*=CH$_2$), 6.70 (CH=N), 6.77-7.26 (11 H, ov, 7-H and Ph), 7.48 (1 H, d, *J*= 8.6 Hz, 9-H), 7.72 (1 H, dd, *J*= 6.6, 8.6 Hz, 8-H), 8.43 (1 H, br s, NH, exchangable with D$_2$O), 9.03 (1 H, d, *J*= 7.3 Hz, 6-H); ^{13}C NMR = 55.5 (*C*H$_2$CH=CH$_2$), 93.0 (3-C), 114.0 (7-C), 117.7 (CH=*C*H$_2$), 124.9 (9-C), 127.9 (6-C), 132.6 (CH=N), 134.2 (*C*H=CH$_2$), 137.1 (8-C), 113.5, 119.4, 125.4, 126.0, 128.9, 129.1, 145.7, 146.3 (Ph-C), 149.7 (9a-C), 156.5 (2-C), 159.7 (4-C).

2-[*N*-Allyl(benzensulfonyl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-phenylhydrazone (**3g**): red needles from EtOH; mp 153-155 °C; IR (KBr) 3270 (NH), 1680 (CO), 1340, 1160 cm^{-1} (SO$_2$); ^{1}H NMR δ= 4.29 (1 H, d, *J*= 6.6 Hz, C*H*$_2$CH=CH$_2$), 4.95 (1 H, dd, *J*= 1.3, 9.9 Hz, CH$_2$CH=CH*H*), 5.05 (1 H, dd, *J*= 1.3, 17.3 Hz, CH$_2$CH=C*H*H), 5.72 (1 H, m, CH$_2$C*H*=CH$_2$), 6.87-7.96 (14 H, ov, 7-, 8-, 9-H, NH and Ph), 8.18 (1 H, s, CH=N), 9.11 (1 H, d, *J*= 6.9 Hz, 6-H); ^{13}C NMR (DMSO-d$_6$): δ= 51.6 (*C*H$_2$CH=CH$_2$), 109.8 (3-C), 117.3 (7-C), 119.1 (CH$_2$CH=*C*H$_2$), 112.1, 118.7, 128.4, 128.9, 129.0, 133.2, 138.8, 145.4 (Ph-C), 125.6 (9-C), 127.5 (6-C), 131.0 (CH=N), 132.1 (CH$_2$*C*H=CH$_2$), 137.8 (8-C), 147.2 (9a-C), 152.2 (2-C), 156.4 (4-C). Anal. Calcd for $C_{24}H_{21}N_5O$: C, 62.73; H, 4.61; N, 15.24%. Found: C, 62.63; H,4.59; N, 15.05%.

2-[*N*-Allyl(ethoxycarbonyl)amino]-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde *(E)*-phenylhydrazone (**3h**): red needles from hexane-AcOEt; mp 166-167 °C; IR (KBr) 3250 (NH), 1685, 1670 cm^{-1} (C=O); ^{1}H NMR δ= 1.11 (3 H, t, *J*= 6.9 Hz, -CH$_3$), 4.09 (2 H, q, *J*= 6.9 Hz, C*H*$_2$CH$_3$), 4.62 (2 H, d, *J*= 5.9 Hz, C*H*$_2$CH=CH$_2$), 5.03 (1 H, d, *J*= 10.2 Hz, CH$_2$CH=CH*H*), 5.24 (1 H, d, *J*= 17.2 Hz, CH$_2$CH=C*H*H), 6.03 (1 H, m, CH$_2$C*H*=CH$_2$), 6.82-7.30 (6 H, ov, 7-H and Ph), 7.60 (1 H, d, *J*= 8.9 Hz, 9-H), 7.73 (1 H, dd, *J*= 6.6, 8.9 Hz, 8-H), 7.89 (1 H, br s., NH), 8.16 (1 H, s, CH=N), 9.03 (1 H, d, *J*= 6.9 Hz, 6-H); ^{13}C NMR δ= 14.3 (-CH$_3$), 50.9 (*C*H$_2$CH=CH$_2$), 62.2 (*C*H$_2$CH$_3$), 107.6 (3-C), 112.7, 119.8, 129.2, 144.4 (Ph-C), 115.9 (7-C), 117.2 (CH$_2$CH=*C*H$_2$), 126.2 (9-C), 127.3 (6-C), 131.0 (CH=N), 134.0 (CH$_2$*C*H=CH$_2$), 136.0 (8-C), 148.0 (9a-C), 153.9 (CO$_2$), 154.3 (2-C), 158.9 (4-C). Anal. Calcd for $C_{21}H_{21}N_5O$: C, 64.43; H, 5.41; N, 17.89%. Found: C, 64.35; H, 5.44; N, 17.89%.

Thermal Behaviors of the Isolated Hydrazones 3e-h; Typical Procedures: A solution of ***(E)*-3e** (0.0283 g, 0.063 mmol) in EtOH (3 ml) was deoxgenated by introducing argon and heated under reflux for 4 h under argon atmosphere. The solution was cooled with ice-salt bath and the resultant red crystals **5e** (0.0243 g, 86%) was collected by filtration. Similarly, heating of ***(Z)*-3e** in EtOH was required 48 h to complete the reaction and the cooling the reaction mixture and filtration gave **5e** (0.0207 g, 73%).

(2a*R**,5a*S**,13c*S**)-6-Benzyl-13-oxo-2a,3,4,5,5a,6,13,13c-octahydro-2*H*-pyrazolo[3,4,5-*de*]pyrido-[1',2':1,2]pyrimido[2,3-*b*]quinoline (**5e**): red needles from AcOEt; mp 264-266 °C; IR (KBr) 1680 cm^{-1} (CO); ^1H NMR δ= 0.90-2.14 (6 H, ov, 3-, 4- and 5-H), 3.51 (1 H, dd, *J*= 7.3, 7.9 Hz, 13c-H), 3.67 (1 H, m, 2a-H), 4.40 (1 H, m, 5a-H), 4.27, 5.94 (each 1 H, each d, *J*= 15.5 Hz, CH_2Ph), 6.79-7.38 (12 H, ov, 10-, 8-H and Ph), 7.58 (1 H, dd, *J*= 6.6, 8.9 Hz, 9-H), 9.05 (1 H, d, *J*= 6.9 Hz, 11-H); ^{13}C NMR δ= 17.8, 24.7, 26.6 (3-, 4-, and 5-C), 45.9 (5b-C), 49.5 (CH_2Ph), 54.2(5a-C), 59.8 (2a-C), 87.3 (13a-C), 113.0 (10-C), 117.4, 118.5, 127.2, 127.3, 128.6, 128.7, 138.2, 143.2 (Ph-C), 124.2 (8-C), 127.8 (11-C), 136.5 (9-C), 144.9 (13b-C), 149.6 (7a-C), 152.9 (6a-C), 156.0 (13-C). Anal. Calcd for $C_{28}H_{25}N_5O$: C, 75.14; H, 5.63; N, 15.62%. Found: C, 74.67; H, 5.70; N, 15.22%.

(3a*S**,12b*R**)-12-Oxo-2,5-diphenyl-1,2,3,3a,4,5,12,12b-octahydropyrazolo[3,'4':4,5]pyrido[2,3-*b*]-pyrido[1,2-*a*]pyrimidine (**4f**): this compound was obtained as red crystals. However, the analytical sample for **4f** coulld not be accomplished because of its instability. The structure of **4f** was deduced to be the *cis*-fused pyrazolidine by ^1H NMR spectrum of the mixture of **4f** and **5f**. ^1H NMR δ= 2.87 (1 H, m, 3a-H), 3.40 (1H, m, 3-H), 3.67-4.22 (3 H, ov, 3- and 4-H), 4.50 (1H, d, *J*=5.6 Hz, 12b-H), 6.78-7.55 (13 H, ov, 7-, 8-, 9-H and Ph), 8.96 (1 H, d, *J*= 7.3 Hz, 10-H).

12-Oxo-2,5-diphenyl-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidine (**5f**): red needles from CH_2Cl_2-MeOH; mp 277-279 °C; IR (KBr) 1670 cm^{-1} (CO); ^1H NMR δ= 3.25 (1 H, dd, *J*= 9.2, 11.6 Hz, 3-H), 3.92-4.23 (4 H, ov, 3-, 3a- and 4-H), 6.84-7.47 (12 H, ov, 7-, 9-H and Ph), 7.52 (1 H, dd, *J*= 6.6, 8.6 Hz, 8-H), 9.03 (1 H, d, *J*= 6.9 Hz, 10-H); ^{13}C NMR δ= 42.9 (3a-C), 51.7 (3-C), 54.1 (4-C), 88.8 (12a-C), 113.5 (9-C), 113.6, 119.0, 126.3, 127.0, 128.9, 129.0, 144.4, 145.6 (Ph-C), 124.9 (7-C), 127.9 (10-C), 136.5 (8-C), 146.5 (12b-C), 149.5 (6a-C), 153.4 (5a-C), 157.6 (12-C). Anal. Calcd for $C_{24}H_{19}N_5O$: C, 73.26; H, 4.87; N, 17.80%.

(3a*S**,12b*R**)-5-Benzenesulfonyl-12-oxo-2-phenyl-1,2,3,3a,4,5,12,12b-octahydropyrazolo[3,'4':4,5]-pyrido[2,3-*d*]pyrido[1,2-*a*]pyrimidine (**4g**): this compound was obtained as red crystals. However, the analytical sample for **4g** coulld not be accomplished because of its instability. The structure of **4g** was deduced to be the *cis*-fused pyrazolidine by ^1H NMR spectrum of the mixture of **4g** and **5g**. ^1H NMR δ= 2.94 (1 H, m, 3a-H), 3.47-4.03 (3 H, ov, 3- and 4-H), 4.43 (1 H, dd, *J*= 5.9 Hz, 12b-H), 4.54 (1 H, dd, *J*= 5.0, 12.5 Hz, 4-H), 6.78-8.14 (13 H, ov, 7-, 8-, 9-H and Ph), 8.96 (1 H, d, *J*= 6.9 Hz, 10-H).

5-Benzenesulfonyl-12-oxo-2-phenyl-2,3,3a,4,5,12-hexahydropyrazolo[3,'4':4,5]pyrido[2,3-*d*]pyrido-[1,2-*a*]pyrimidine (**5g**): red needles from EtOH-CH_2Cl_2; mp 281-282 °C; IR (KBr) 1690 (CO), 1350, 1170 cm^{-1} (SO_2); ^1H NMR δ= 3.38 (1 H, dd, *J*= 9.9, 12.5 Hz, 3-H), 3.57 (1 H, dd, *J*= 11.6, 12.2 Hz, 4-H), 3.85 (1 H, m, 3a-H), 4.26 (1 H, dd, *J*= 9.9, 10.2 Hz, 3-H), 5.21 (1 H, dd, *J*= 5.3, 11.6 Hz, 4-H), 6.86-8.12 (13 H, ov, 7-, 8-, 9-H and Ph), 9.00 (1 H, d, *J*= 6.3 Hz, 10-H); ^{13}C NMR δ= 43.6 (3a-C), 48.0 (4-C), 51.4, (3-C), 93.0 (12a-C), 113.5, 119.7, 128.0, 128.3, 128.6, 129.0, 141.0, 143.8 (Ph-C), 115.5 (9-C), 124.9 (7-C), 133.3 (10-C), 137.2 (8-C), 145.8 (12b-C), 147.9 (6a-C), 153.3 (5a-C), 153.8 (12-C). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 63;00; H, 4.19; N, 15.31%. Found: C, 63.01; H, 4.24; N, 15.29%.

Kinetic Studies. The apparatuses and procedures for the measurement of the conversion rates are same as those in the preceding paper.[7f] To measure the rates of disappearance of hydrazones, anisole for hydrazones ***(E)***- and ***(Z)*-3e** and **3f** and dichlorobenzene for hydrazone **3g** were utilized as internal standards, respectively. A Wakosil-II5C18HG (id 4.6 mm x 250 mm) column was used and the flow rate of the elution was 1 ml min^{-1}. The components of the elution were acetonitrile-H_2O (85:15) for hydrazones ***(E)***- and ***(Z)*-3e** and acetonitrile-H_2O (70:30) for hydrazones **3f** and **3g**. All rates of conversion of hydrazones **3** under several conditions (temperature, solvent, and additive) were first order with respect to the hydrazone concentration.

The obtained rate constants [k (s^{-1}) x 10^5] were as bellows: for ***(E)*-3e** in dioxane at 6.67 x 10^{-4} M, 0.900 (50.7 °C), 2.55 (56.3 °C), 6.94 (68.8 °C), 1.01 [Et_3N (2.0 equiv.), 50.7 °C], 1.11 [at 6.67 x 10^{-3} M, 50.7 °C], and 1.53 x 10^3 [PTSA (0.2 equiv.), 50.7 °C]; for ***(Z)*-3e** in dioxane at 6.67 x 10^{-4} M, 0.873 (78.3 °C), 1.54 (87.2 °C), 3.69 (97.2 °C), and 67.86 [PTSA (2.0 equiv.), 78.3 °C]; for **3f** in dioxane at 7.59 x 10^{-4} M, 1.59 (68.8 °C); for **3g** in dioxane at 6.53 x 10^{-4} M, 0.776 (77.1 °C), 1.08 (87.2 °C), 1.85 (97.2 °C), and 21.82 [PTSA (2.0 equiv.), 97.2 °C); for **3g** in DMF at 6.53 x 10^{-4} M, 3.07 (97.2 °C); for **3g** in butan-1-ol at 6.53 x 10^{-4} M, 1.86 (78.3 °C), 2.67 (82.2 °C), 4.01 (87.2 °C), and 8.58 (97.2 °C). The relative rates and activation parameters for the conversion of ***(E)***- and ***(Z)*-3e** and the relative rates of ***(E)***- and ***(Z)*-3e**, **3f**, and **3g** and activation parameters of **3g** are summarized in Tables 3 and 4, respectively.

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