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Mechanistic Considerations on the Azepine-Ring Formation through the Ene Reactions at the Periphery of Heterocyclic Systems

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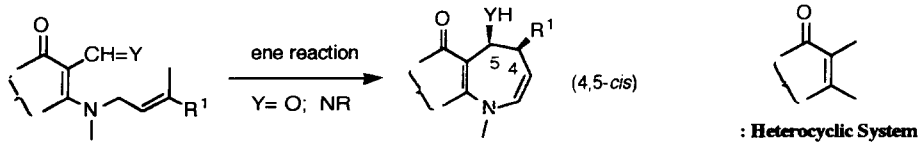
Abstract: A mechanistic proposal for the azepine-ring formation at the periphery of heterocyclic systems is described. Intramolecular thermal ene reactions of *O*-alkyl oximes **5** and **6**, *N',N'*-disubstituted hydrazone **11**, and *N*-tosyl imines, obtained from aldehydes of pyrido[1,2-*a*]-pyrimidine **1**, pyridine **2**, and pyrimidine system **3**, have been developed. These reactions reveal to be a fruitful and stereoselective approach to the azepine derivatives fused by heterocycles. The mechanistic discussions on the azepine-ring formation through the imine and carbonyl ene reactions have been accomplished by the kinetic studies as well as the molecular orbital calculations (PM3 method) of the model reactions. These results demonstrate that both ene reactions proceed in a concerted manner. Copyright © 1996 Elsevier Science Ltd

Introduction

In the preceding paper[1] and previous ones,[2,3] we reported interesting azepine-ring formation through the thermal imine and/or carbonyl ene reactions at the periphery of pyridine,[1] pyrido[1,2-*a*]pyrimidine,[1] pyrimidine,[2] and 1-benzopyran systems[3] as shown in Scheme 1. Therein, the all imine substrates could not be isolated and were utilized by the reaction of the corresponding aldehydes with primary amines *in situ*. This resulted in an ambiguity in the discussion of the reactivities between carbonyl and imine ene reactions. In order to obtain better understandings and to extend the scope of the imine ene reaction in these systems, we examined the thermal reactions of the *O*-substituted oximes, *N',N'*-disubstituted hydrazone, and *N*-tosyl imines of the aldehydes. These substrates could be regarded as imines substituted by heteroatom on the imine nitrogen and isolated in pure forms except for the *N*-tosyl imines. The above imines also underwent the azepine-ring formation but were less reactive than the imines substituted by alkyl or aryl groups on the imine nitrogen.[1,2] Some mechanistic discussions on the azepine-ring formation through the carbonyl and imine ene reactions will be described on the basis of their kinetic studies as well as molecular orbital (MO) calculations.

Scheme 1.



Azepine-ring Formation through the Ene Reaction of Imines Substituted by Heteroatoms on the Imine Nitrogen

The reaction of 2-(*N*-allylbenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine 3-carboxaldehyde (**1a**) with *O*-methyl- (**4a**) and *O*-benzyl-hydroxylamine hydrochloride (**4b**) in some solvents gave inseparable mixtures of

Scheme 2.

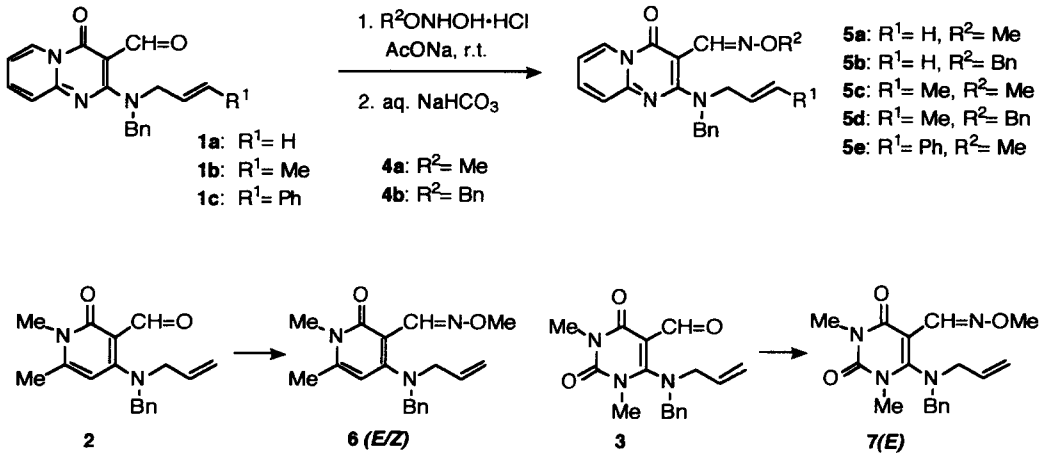


Table 1. Preparation of *O*-Alkyl Oximes **5**, **6**, and **7** from Aldehydes **1-3** with *O*-Alkylhydroxylamines **4**

Entry	Substrates	R^1	R^2	Solvent	Time (h)	Product/ Yield (%)[a]	Ratio[b] of *E* : *Z*
1	**1a** + **4a**	H	Me	MeOH	3	**5a** / quant.	99 : 1
2	**1a** + **4a**	H	Me	benzene	20	**5a** / 86	66 : 34
3	**1a** + **4a**	H	Me	MeCN	20	**5a** / quant.	85 : 15
3	**1a** + **4b**	H	Bn	MeOH	3.5	**5b** / quant.	98 : 2
4	**1b** + **4a**	Me	Me	MeOH	3.5	**5c** / quant.	100 : 0
5	**1b** + **4b**	Me	Bn	MeOH	4	**5d** / quant.	91 : 9
6	**1c** + **4a**	Ph	Me	MeOH	7 day	**5e** / quant.	85 : 15
7	**2** + **4a**			MeOH	5.5	**6** / 92	98 : 2
8	**3** + **4a**			MeOH	2	**7** / 91	100 : 0

[a] Based on the isolated products. [b] Determined by ^{1}H NMR spectra of the crude products.

E- and *Z*-isomers of the *O*-methyl oxime **5a** and *O*-benzyl oxime **5b**. While *O*-methyl oxime **5c** was obtained in a similar way as a *E*-isomer, *O*-benzyl oxime **5d** and *O*-methyl one **5e** existed as mixtures of *E* and *Z*-isomers. The configurations of the isomers were determined on the basis of the chemical shifts of the imine proton signals according to the assignment reported;[4] the imine proton signals of the *E*-isomers were observed at δ 8.3-8.5, while those of the *Z*-isomers at δ 7.8. The ratios of the isomers depended mainly on the solvents utilized; the reaction in benzene gave about a 2:1 mixture and in methanol gave almost pure *E*-isomer. Similar treatment of 4-(*N*-allylbenzylamino)-1,6-dimethyl-2-oxo-1*H*-pyridine 3-carboxaldehyde (**2**) and 6-(*N*-allylbenzylamino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine 5-carboxaldehyde (**3**) with *O*-methylhydroxylamine hydrochloride (**4a**) gave oximes **6** and **7** (Scheme 2 and Table 1).

The deoxygenated solution of *O*-methyl oxime **5a** (*E*/*Z*= 97:3) in *o*-dichlorobenzene (ODCB) was heated under reflux and usual work-up gave a 69:31 mixture of 5-methoxyamino-1-benzyl-4,5-dihydropyrido-[1',2':1,2]pyrimido[4,5-*b*]azepin-6(1*H*)-one (**8a**) and 1-benzyl-3-methoxy-3,4-dihydro-2,4-ethano-2*H*-pyrido-[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-5(1*H*)-one (**9a**) in total 91% yield. The *E*:*Z* ratio of the recovered **4a** (7%) was determined to be 47:53. Azepine **8a** was not so stable and converted gradually to ethanopyridopyrimido-pyrimidine **9a** during the further purification with silica gel column or the prolonged heating of its ODCB solution

(Table 2, Entry 2). A similar transannulation of the azepine derivatives was observed in previous works.[1,2]

Thermal reaction of oximes **5b-e** and **6** gave also fused pyrimidines **9b-e** and **10** in fair to good yields and products **9c-e** were obtained also as single diastereoisomers (Scheme 3). The progress of these reactions in 2-methoxyethyl ether (diglyme) was monitored by HPLC (see the Experimental section) and revealed that only *E*-isomers of the oximes underwent the above cyclizations and *Z*-isomers were unchanged.[5] No interconversion between *E*- and *Z*-isomers of the oximes was observed under these conditions. On the other hand, a similar reaction of oxime **7** gave many products owing to decomposition. These results are summarized in Table 2.

Scheme 3.

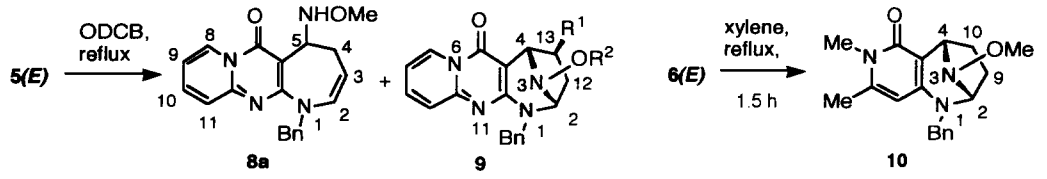


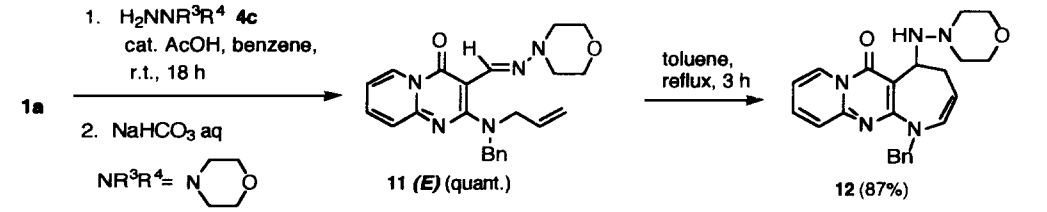
Table 2. Azepine-ring Formation through the Imine Ene Reaction of *N*-Alkyl Oximes **5** and **6**

Entry	Substrate	R^1	R^2	Ratio of *E* : *Z*	Time/h	Product/ Yield (%)[b]	Recovered starting material/ Yield (%)	Ratio[a] of *E* : *Z*
1	**5a**	H	Me	97 : 2	1	**8a** + **9a** / 91[c]	**5a** / 7	45 : 53
2	**5a**	H	Me	99 : 1	2	**9a** / 94		
3	**5a**	H	Me	43 : 57	24	**9a** / 41	**5a** /43	8 : 92
4	**5b**	H	Bn	98 : 2	4	**9b** / 91		
5	**5c**	Me	Me	100 : 0	5.5	**9c** / 79		
6	**5d**	Me	Bn	91 : 9	4	**9d** / 81		
7	**5e**	Ph	Me	85 : 15	2.5	**9e** / 61		
8	**6**			97 : 3	1.5	**10** / 81		

a) Based on the isolated products. b) The ratio of **8a** and **9a** was confirmed to be 69:31 from ^{1}H NMR spectrum of the crude mixuture.

These prompted us to investigate the reaction of a hydrazone of aldehyde **1a**. Heating the xylene solution of 2-(*N*-allylbenzylamino)-3-(morpholinoimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**11**) gave azepine **12** in good yield (Scheme 4).

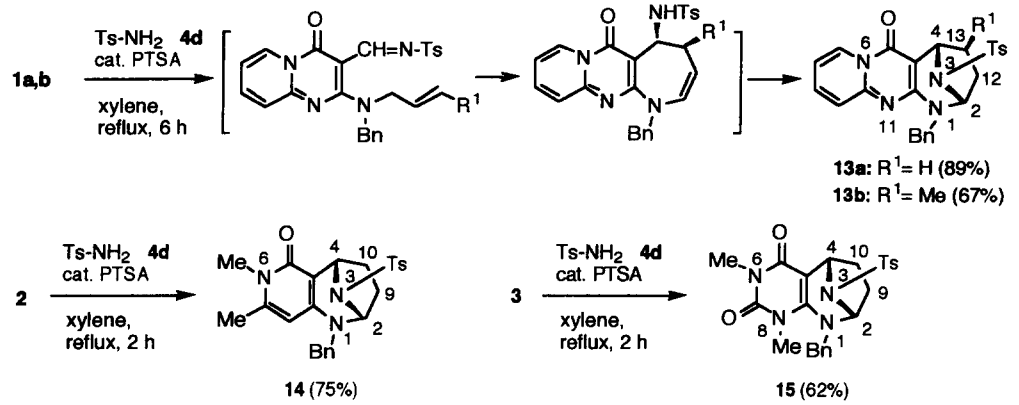
Scheme 4.



Previously, Weinreb[6] reported the ene reaction of an *N*-tosyl imine without catalyst; an adduct from crotyl glyoxylate and tosylamide was heated in ODCB under reflux giving the *N*-tosyl imine of crotyl glyoxylate, which underwent the imine ene reaction to afford a butyrolactone derivative. Therefore, we also examined the thermal

reaction of the aldehyde **1a** with tosylamide (**4d**) in several conditions to give disappointing results. Utilizing *p*-toluenesulfonic acid (PTSA) as a dehydrating reagent provided a good fortune; a solution of aldehyde **1a**, tosylamide (**4d**), and a catalytic amount of PTSA in xylene was heated under reflux to give fused pyrimidine **13a** in 89% yield as a final product of the imine ene reaction. Similar treatment of aldehydes **1b**, **2**, and **3** with tosylamide (**4d**) in the presence of PTSA gave the expected products **13b**, **14**, and **15**, respectively (Scheme 5). Probably, the *N*-tosyl imine intermediates are expected to have a high reactivity for the azepine-ring formation[7] and the step of imine formation should be crucial.

Scheme 5.



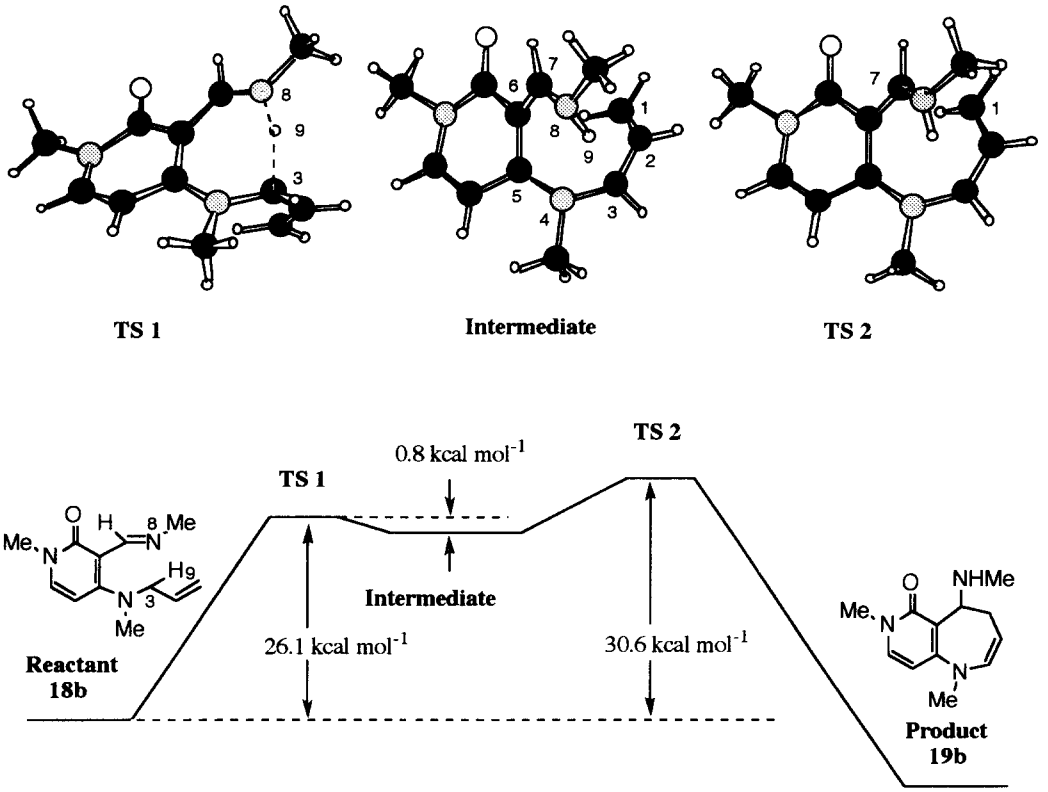
Although higher reaction temperatures were required to complete the azepine-ring formation of oximes **5** and **6** and hydrazone **11** than those of the corresponding imines,[1,2] the ene reactions utilizing various types of imines as enophiles are useful for the stereoselective synthesis of azepines fused by heterocyclic systems.

Mechanistic Considerations for Imine and Carbonyl Ene Reactions

We examined the semi-empirical MO calculations utilizing PM3 method[8] in MOPAC program[9] for the cyclization processes. To avoid conformational and computational complexities, the calculations were performed for the conversion of *N*-allylmethylamino substrates at the periphery of pyridopyrimidine **16**, and pyridine **18**, pyrimidine **20**, and pyran system **22** to the corresponding azepine derivatives **17**, **19**, **21**, and **23**, respectively. The differential reactivities between the carbonyl and imine ene reaction and the effects of the substituents (Y= NR^2; **b**: R^2= Me; **c**: R^2= OMe; **d**: R^2= NMe_2) on the imine nitrogen on the ene reactions were examined. The potential energy surfaces of the processes were consistent with those of the conversion of 4-(*N*-allylmethylamino)-2-oxo-2*H*-pyran 3-carboxaldehyde (**22a**) to 1-methyl-5-hydroxy-4,5-tetrahydropyrano[4,3-*b*]azepin-6(1*H*)-one (**23a**) reported in the previous paper.[3] The diagrams reveal that these reactions proceed with the consecutive two steps; the first one is a [1,6]-shift of the allylic hydrogen to the carbonyl oxygen or the imine nitrogen leading to an intermediate. The calculated structure[10] of the first transition state (TS 1) for the processes correspond the transition states for the antarafacial hydrogen shifts similarly to the 1,7-sigmatropic rearrangement in the 8π-electrons system. The intermediate is a minimum[11] in the potential energy surface close to TS 1 and its structure could be regarded as a conjugated azomethine ylide. The second step (TS 2) is the 1,7-electrocyclic ring-closure of the conjugated azomethine ylide bearing 8π-electrons[12] in a conrotatory manner[13] (Fig. 1). In some systems, the potential energy surfaces in the vicinity of TS 1 are so flat and the energy gaps between the TS 1 and the intermediates are so small[14] that the first steps (TS 1) and/or intermediates could not be

identified. This suggested that the azepine-ring formation through ene reactions proceeded nearly in a concerted manner. The activation enthalpies based on the heats of formation of the reactant, TS 1, intermediate, and TS 2 for the conversions of the model reactions are summarized in Table 3.

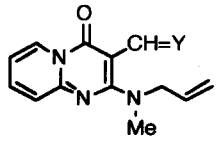
Fig. 1. Schematic Energy Diagram and Structures of TS 1, Intermediate, and TS 2 for the Ene Reaction of *N*-Methyl Imine **18b**



As shown in Table 3, the imine ene reaction is superior to the corresponding carbonyl one in the same heterocyclic system. No apparent solvent effects of both imine and carbonyl ene reactions are due to small changes of the atomic charges[10] between the reactants and TS 2. Among the imines **16b-d**, the *N*-methyl substrate **16b** is expected to be most reactive for the ene reaction (Entries 2-4). As described before, the reactivity of the *O*-methyl oximes depended on their *E*- and *Z*-configurations. This is also explained by the calculation results; the TS 1 for oxime **18c*(Z)***, the rate determining step in this process, is estimated to be higher by 15.2 kcal mol^{-1} than that for the *E*-isomer, **18c *(E)*** (Entries 7 and 8). The effect of the electron-withdrawing substituent on the amino nitrogen on the carbonyl ene reactivity was examined; *N*-formylallylamino substrate **18e** (Y= O; R^5= CHO) could not be expected to undergo the ene reaction in the same conditions as those for *N*-methyl substrate **18a** because of the too elevated TS 2; higher by 8.2 kcal mol^{-1} than that for **18a** (Entry 8). Both carbonyl and imine ene reactions in all the heterocyclic systems bearing a *trans*-alkenyl ene moiety proceeded in a stereoselective manner to afford 4,5-*cis* azepine derivatives except for pyrimidine one, in which a

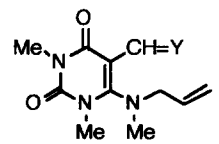
mixture of 4,5-*cis* and -*trans* isomers was obtained.[2] Although the exact details of the formation of 4,5-*trans* azepine are still obscure, a plausible explanation can be given; the more stabilized azomethine ylide intermediate in the pyrimidine system might provide another path with a less 4,5-*cis* selectivity (Entry 10).

Table 3. Activation Enthalpies for the Model Reaction of Pyridopyrimidines **16**, Pyridines **18**, Pyrimidine **20**, and Pyrans **22** Estimated from the Heats of Formation of Their Reactants, TS 1, Intermediates, and TS 2 by PM3 Method.

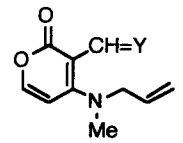


16a: Y= O
16b: Y= N-Me
16c: Y= N-OMe
16d: Y= N-NMe_2

18a: R^5= Me; Y= O
18b: R^5= Me; Y= N-Me
18c: R^5= Me; Y= N-OMe
18e: R^5= CHO; Y= O



20b: Y= N-Me



22a: Y= O
22b: Y= N-Me

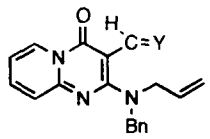
		Activation Enthalpy $\Delta H^{\ddagger}$ (kcal mol^{-1})		
Entry	Reactant	TS 1	Intermediate	TS 2
1	**16a**	NI[a)]	NI	34.7
2	**16b(*E*)**	NI	24.0	28.0
3	**16c(*E*)**	NI	24.3	29.1
4	**16d(*E*)**	27.7	26.9	31.9
5	**18a**	29.9	29.4	34.9
6	**18b(*E*)**	26.1	25.3	30.6
7	**18c(*E*)**	27.6	24.9	30.8
8	**18c(*Z*)**	44.8	29.0	35.3
9	**18e**	NI	NI	43.1
10	**20b(*E*)**	26.6	20.9	28.7
11	**22a**[b)]	27.1	26.5	33.6
12	**22b(*E*)**	23.1	22.2	27.6

a) NI: Not identified. b) See ref. (3).

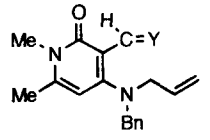
Finally, the activation enthalpies demonstrated in Table 3 should be overestimated taking the following findings into consideration; most of the ene reactions of *N*-alkyl and *N*-aryl imines were accomplished under considerably mild conditions, *e.g.*, in refluxing benzene or toluene.[1,2] As mentioned before, the *O*-alkyl oximes **5** and **6** and *N',N'*-disubstituted hydrazone **11**, imines substituted by heteroatom on the imine nitrogen, were less reactive than the corresponding ordinary imines. The calculated activation enthalpies (TS 2; more than 28 kcal mol^{-1}) for the conversion of *N*-methyl imines **18b**, **20b**, and **22b** to azepines **19b**, **21b**, and **23b** seem to be too large by comparison with our experiences. Similar overestimation of activation enthalpies by PM3 calculations was found in the literature.[15] We, therefore, examined the kinetics using aldehydes and their imine derivatives by a HPLC method (see the Experimental section). The reaction rates of aldehydes **1a** and **2** and their *O*-methyl oximes **5a** and **6** were measured in diglyme at several temperatures. In all cases the rates of the disappearance of the aldehydes and oximes were of first-order with respect to their concentrations. The activation energies and parameters are summarized in Table 4.

The effects of the solvents utilized on the rates of the conversion of **1a** and **5a** were also examined. Replacing diglyme with pentan-1-ol and DMF as reaction solvents gave small changes of the reaction rates for oxime **5a** (the relative rate was 1.00 in diglyme, 0.70 in pentan-1-ol, and 1.05 in DMF). Contrastly, the rate of the conversion for aldehyde **1a** in a polar solvent was slightly depressed; the relative rate was 1.00 in diglyme, 0.87 in pentan-1-ol, and 0.39 in DMF (see the Experimental section). As a whole, the azepine-ring formation from both the aldehydes and imines did not show apparent solvent effects.

Table 4. Activation Energy and Activation Parameters for the Thermal Reaction of Aldehydes **1a** and **2**, Oximes **5a** and **6** in Diglyme.



1a: Y= O
5a: Y= N-OMe



2: Y= O
6: Y= N-OMe

Entry	Reactant	Activation Energy *Ea* (kcal mol^{-1})	Activation Enthalpy $\Delta H^{\ddagger}$ (kcal mol^{-1})a)	Activation Entropy $\Delta S^{\ddagger}$ (cal K^{-1})a)
1	**1a**	26.7	26.5	- 17.3
2	**5a**	24.3	21.8	- 15.4
3	**2**	20.6	20.6	- 39.8
4	**6**	19.2	16.8	- 51.7

a) At the standard state.

Conclusion

We have described the azepine-ring formations utilizing various types of imines at the periphery of heterocyclic systems. Therein, the oximes, hydrazone, and *N*-tosyl imines also undergo the azepine-ring formations through the ene reactions. The results of kinetic studies and PM3 calculations using the aldehydes and their imines suggest a concerted nature of the azepine-ring formation.

Experimental Section

General Methods. Descriptions of instruments, general procedures, and chromatographic procedures have been published previously.[1]

Preparation of *O*-Substituted Oxime Substrates 5, 6, and 7. Typical Procedures: A solution of aldehyde **1a** (0.193 g, 0.60 mmol), *O*-methylhydroxylamine hydrochloride (**4**; 0.065 g, 0.78 mmol), and sodium acetate (0.074 g, 0.90 mmol) in methanol (5 ml) was stirred at room temperature for 3 h. The solvent was evaporated to dryness, which was treated with 5% sodium hydrogen carbonate (30 ml) and extracted with dichloromethane (3 x 30 ml). The organic layer was collected and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the corresponding *O*-methyl oxime **5a** (0.209 g, quant.) as a 98:2 mixture of *E*- and *Z*-isomer.

2-(*N*-Allylbenzylamino)-3-(methoxyimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5a**): yellow oil; IR (NaCl) 1660 cm^{-1}. Anal. Found: C, 68.79; H, 5.85; N, 15.84%. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%. *E*-Isomer: ^1H NMR ($CDCl_3$) δ= 3.92 (3 H, s, OMe), 4.11 (2 H, d, *J*= 5.9 Hz, $NCH_2CH=CH_2$), 4.85 (2 H, s, CH_2Ph), 5.08-5.29 (2 H, ov, $NCH_2CH=CH_2$), 5.79 (1 H, m, $NCH_2CH=CH_2$), 6.81-7.64 (8 H, ov, Ph and 7-, 8- and 9-H), 8.35 (1 H, s, -CH=N-), 8.87 (1 H, ddd, *J*= 0.7, 1.7, 6.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 52.6, 53.0 (CH_2Ph and $NCH_2CH=CH_2$), 61.7 (OMe), 89.8 (3-C), 113.1 (7-C), 118.1 (-CH=CH_2), 124.6 (9-C), 127.1, 127.8, 128.4, 137.7 (Ph-C), 127.7 (6-C), 133.7 -$CH=CH_2$), 136.7 (8-C), 145.5 (-CH=N-), 148.6 (9a-C), 158.1 (2-C), 160.3 (4-C). *Z*-Isomer: ^1H NMR ($CDCl_3$; assigned signals) δ= 3.82 (3 H, s, OMe), 4.07 (2 H, d, *J*= 5.9 Hz, $NCH_2CH=CH_2$), 4.82 (2 H, s, CH_2Ph), 7.80 (1 H, s, -CH=N-), 8.80 (1 H, ddd, *J*= 0.7, 1.7, 6.3 Hz, 6-H).

2-(*N*-Allylbenzylamino)-3-(benzyloxyimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5b**): yellow oil; IR (NaCl) 1660 cm^{-1}. Anal. Found: C, 73.82; H, 5.80; N, 12.93%. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20%.

E-Isomer: ^1H NMR ($CDCl_3$) δ= 4.00 (2 H, d, *J*= 5.9 Hz, $NCH_2CH=CH_2$), 4.72 (2 H, s, NCH_2Ph), 5.01-5.10 (2 H, ov, $NCH_2CH=CH_2$), 5.13 (2 H, s, OCH_2Ph), 5.72 (1 H, m, $NCH_2CH=CH_2$), 6.83 (1 H, dt, *J*= 1.3, 6.9 Hz, 7-H), 7.17-7.56 (12 H, ov, Ph and 8- and 9-H), 8.50 (1 H, s, -CH=N-), 8.82 (1 H, d, *J*= 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 52.9, 53.0 (NCH_2Ph and $NCH_2CH=CH_2$), 76.1 (OCH_2Ph), 90.0 (3-C), 113.3 (7-C), 118.2 (-CH=CH_2), 124.8 (9-C), 127.3, 127.8, 128.1, 128.6, 128.7, 138.1, 138.6 (Ph-C), 127.9 (6-C), 134.0 (-$CH=CH_2$), 137.0 (8-C), 146.4 (-CH=N-), 148.8 (9a-C), 158.7 (2-C), 160.2 (4-C). *Z*-Isomer: ^1H NMR ($CDCl_3$; assigned signals) δ= 3.95 (2 H, d, *J*= 5.9 Hz, $NCH_2CH=CH_2$), 4.67 (2 H, s, NCH_2Ph), 5.07 (1 H, s, OCH_2Ph), 7.79 (1 H, s, -CH=N-).

2-[*N*-Benzyl(*trans*-crotyl)amino]-3-(methoxyimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5c**): pale yellow oil; IR (NaCl) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.68 (3 H, d, *J*= 5.3 Hz, $NCH_2CH=CHMe$), 3.92 (3 H, s, OMe), 4.02 (2 H, d, *J*= 5.6 Hz, $NCH_2CH=CHMe$), 4.84 (2 H, s, CH_2Ph), 5.42-5.63 (2 H, ov, $NCH_2CH=CHMe$), 6.86 (1 H, br t, *J*= 6.5 Hz, 7-H), 7.20-7.35 (6 H, ov, Ph and 9-H), 7.53-7.60 (1 H, m, 8-H), 8.34 (1 H, s, -CH=N-), 8.87 (1 H, ddd, *J*= 0.7, 1.7, 6.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 17.7 (Me), 52.0, 52.5 (CH_2Ph and $NCH_2CH=CH_2$), 61.6 (OMe), 89.5 (3-C), 112.9 (7-C), 124.5 (9-C), 126.2 (-CH=CHMe), 126.9, 127.7, 128.2, 137.8 (Ph-C), 129.7 (-CH=CHMe), 136.6 (8-C), 145.5 (-CH=N-), 148.5 (9a-C), 158.0 (2-C), 160.2 (4-C). Anal. Found: C, 69.77; H, 6.25; N, 15.15%. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H. 6.12; N, 15.46%.

2-[*N*-Benzyl(*trans*-crotyl)amino)-3-(benzyloxyimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5d**): yellow oil ; IR (NaCl) 1660 cm^{-1}. Anal. Found: C, 74.20; H, 6.09; N, 12.67%. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78%.

E-Isomer: ^1H NMR ($CDCl_3$) δ= 1.65 (3 H, d, *J*= 5.6 Hz, $NCH_2CH=CHMe$), 3.91 (2 H, d, *J*= 5.6 Hz, $NCH_2CH=CHMe$), 4.73 (2 H, s, NCH_2Ph), 5.13 (2 H, s, OCH_2Ph), 5.34-5.51 (2 H, ov, -CH=CH_2), 6.82 (1 H, t, *J*= 7.3 Hz, 7-H), 7.19-7.35 (10 H, ov, Ph), 7.38 (1 H, d, *J*= 7.3 Hz, 9-H) 7.52 (1 H, t, *J*= 7.3 Hz, 8-H), 8.47 (1 H, s, -CH=N-), 8.83 (1 H, d, *J*= 7.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 17.8 (-CH=$CHMe$), 52.1, 52.4 (NCH_2Ph and $NCH_2CH=CHMe$), 75.8 (OCH_2Ph), 89.6 (3-C), 112.8 (7-C), 124.5 (-CH=CHMe), 126.3 (9-C), 126.9 (6-C), 127.6, 127.7, 128.2, 128.3, 137.9, 138.2 (Ph-C), 129.5 (-CH=CHMe), 136.6 (8-C), 146.1 (-CH=N-), 148.4 (9a-C), 158.3 (2-C), 159.9 (4-C). *Z*-Isomer: ^1H NMR ($CDCl_3$; assigned signals) δ= 4.66 (2 H, s, NCH_2Ph), 5.06 (2 H, s, OCH_2Ph), 7.79 (1 H, s, -CH=N-).

2-[*N*-Benzyl(*trans*-cinnamyl)amino]-3-(methoxyimino)methylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5e**): pale yellow oil; IR (NaCl) 1660 cm^{-1}. Anal. Found: C, 73.43; H, 5.92; N, 12.72%. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20%.

E-Isomer: ^{1}H NMR ($CDCl_3$) δ= 3.92 (3 H, s, OMe), 4.26 (2 H, d, *J*= 6.3 Hz, NCH_2CH=CHPh), 4.88 (2 H, s, CH_2Ph), 6.22 (1 H, td, *J*= 6.3, 15.8 Hz, NCH_2CH=CHPh), 6.46 (1 H, d, *J*= 15.8 Hz, -CH=CHPh), 6.90 (1 H, dd, *J*= 1.3, 6.9 Hz, 7-H), 7.17-7.35 (11 H, ov, Ph and 9-H), 7.61 (1 H, dd, *J*= 1.3, 6.9 Hz, 8-H), 8.41 (1 H, s, -CH=N-), 8.82 (1 H, d, *J*= 6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 52.5, 52.8 (CH_2Ph and NCH_2CH=CH_2), 61.7 (OMe), 89.8 (3-C), 113.1 (7-C), 124.6 (9-C), 125.2, 127.1, 127.6, 127.8, 128.4, 128.5, 136.6, 137.6 (Ph-C), 126.3 (-CH=CHPh), 127.7 (6-C), 133.3 (-CH=CHPh), 136.7 (8-C), 145.5 (-CH=N-), 148.6 (9a-C), 158.2 (2-C), 160.2 (4-C). *Z*-Isomer: ^{1}H NMR ($CDCl_3$; assigned signals) δ= 3.91 (3 H, s, OMe), 4.24 (2 H, d, *J*= 6.3 Hz, NCH_2CH=CH_2), 4.85 (2 H, s, CH_2Ph), 6.11 (1 H, td, *J*= 6.3, 15.8 Hz, -CH=CHPh), 6.83 (1 H, dd, *J*= 1.3, 6.9 Hz, 7-H), 7.58 (1 H, dd, *J*= 1.3, 6.9 Hz, 8-H), 7.84 (1 H, s, -CH=N-), 8.75 (1 H, d, *J*= 6.9 Hz, 6-H).

4-(*N*-Allylbenzylamino)-3-(methoxyimino)methyl-1,6-dimethylpyridin-2(1*H*)-one (**6**): yellow oil; IR (NaCl) 1660 cm^{-1}. Anal. Found: C, 70.01; H, 7.13; N, 12.85%. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91%.

E-Isomer: ^{1}H NMR ($CDCl_3$) δ= 2.26 (3 H, s, 6-Me), 3.44 (3 H, s, 1-Me), 3.79 (2 H, d, *J*= 5.9 Hz, NCH_2CH=CH_2), 3.92 (3 H, s, OMe), 4.43 (2 H, s, CH_2Ph), 5.16 (1 H, dd, *J*= 1.3, 16.8 Hz, NCH_2CH=CHH), 5.17 (1 H, dd, *J*= 1.3, 10.2 Hz, NCH_2CH=CHH), 5.77 (1 H, m, NCH_2CH=CH_2), 5.85 (1 H, s, 5-H), 7.18-7.33 (5 H, ov, Ph), 8.35 (1 H, s, -CH=N-); ^{13}C NMR ($CDCl_3$) δ= 21.3 (6-Me), 30.7 (1-Me), 54.7, 54.9 (CH_2Ph and NCH_2CH=CH_2), 61.4 (OMe), 101.0 (5-C), 102.3 (3-C), 118.1 (-CH=CH_2), 127.1, 127.5, 128.4, 145.4 (Ph-C), 133.5 (-CH=CH_2), 137.3 (6-C), 146.5 (-CH=N-), 156.6 (4-C), 163.3 (2-C). *Z*-Isomer: ^{1}H NMR ($CDCl_3$; assigned signals) δ= 3.91 (3 H, s, OMe), 4.33 (2 H, s, CH_2Ph), 7.68 (1 H, s, -CH=N-).

6-(*N*-Allylbenzylamino)-5-(methoxyimino)methyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (**7**): colorless prisms from hexane and benzene; mp 74-76 °C; IR (KBr) 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 3.35 (3 H, s, 1-Me), 3.38 (3 H, s, 3-Me), 3.59 (2 H, d, *J*= 6.9 Hz, NCH_2CH=CH_2), 3.93 (3 H, s, OMe), 4.16 (2 H, s, CH_2Ph), 5.20-5.30 (2 H, ov, NCH_2CH=CH_2), 5.85 (1 H, m, NCH_2CH=CH_2), 7.17-7.35 (5 H, ov, Ph), 8.06 (1 H, s, -CH=N-); ^{13}C NMR ($CDCl_3$) δ= 28.3 (1-Me), 33.7 (3-Me), 55.1, 55.7 (CH_2Ph and NCH_2CH=CH_2), 61.7 (OMe), 98.1 (5-C), 119.6 (-CH=CH_2), 127.9, 128.7, 128.8, 133.1 (Ph-C), 136.3 (-CH=CH_2), 143.2 (-CH=N-), 152.1 (6-C), 155.3 (4-C), 162.4 (2-C). Anal. Found: C, 63.01; H, 6.39; N, 16.51%. Calcd for $C_{18}H_{22}N_4O_3$: C, 63.14; H, 6.48; N, 16.36%.

Azepine-Ring Formation from Oximes 5, 6, and 7. Typical Procedure: A solution of oxime **5a** (0.184 g, 0.53 mmol) in ODCB (5 ml) was deoxygenated with argon for 2 h and heated under reflux for 2 h. The solvent was removed *in vacuo* and the residue was treated with column chromatography on silica gel with hexane/ethyl acetate (= 3:1) to afford a 69:31 mixture of azepine **8a** and ethanopyridopyrimidopyrimidine **9a** (0.174 g, 91%) and the recovered **5a** (0.013 g, 7%). Azepine **8a** was spontaneously converted to **9a** during further purification procedures.

1-Benzyl-5-methoxyamino-4,5-dihydropyrido[1',2':1,2]pyrimido[4,5-*b*]azepin-6(1*H*)-one (**8a**): colorless needles from hexane-benzene; mp 103-104 °C; IR (KBr) 3200 (NH), 1660 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 2.51 (1 H, m, 4-H), 2.80 (1 H, m, 4-H), 3.60 (3 H, s, OMe), 5.00 (1 H, m, 3-H), 5.19, 5.24 (each 1 H, each d, J_{gem}= 15.5 Hz, CH_2Ph), 5.32 (1 H, br, 5-H), 5.96 (1 H, br, exchangable with D_2O, 5-NH), 6.10 (1 H, dd, $J_{2\text{-}4}$= 2.3, $J_{2\text{-}3}$= 9.6 Hz, 2-H), 6.89 (1 H, dd, $J_{9\text{-}10}$= 6.6, $J_{8\text{-}9}$= 7.3 Hz, 9-H), 7.23-7.36 (6 H, ov, Ph and 11-H), 7.53 (1 H, dd, $J_{9\text{-}10}$= 6.6, $J_{10\text{-}11}$= 8.3 Hz, 10-H), 8.87 (1 H, d, $J_{8\text{-}9}$= 7.3 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ= 29.4 (4-C), 55.4, 55.5 (CH_2Ph and 5-C), 61.8 (OMe), 99.1 (5a-C), 108.2 (9-C), 113.2 (3-C), 124.9 (11-C), 127.1, 127.7, 128.5, 138.8 (Ph-C), 127.4 (8-C), 131.2 (2-C), 135.7 (10-C), 147.8

(11a-C), 157.5 (12a-C), 158.8 (6-C). Anal. Found: C, 69.14; H, 5.86; N, 16.03%. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%.

1-Benzyl-3-methoxy-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-5(1*H*)-one (**9a**): pale yellow prisms from hexane and benzene; mp 146-148 °C; IR (KBr) 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.86-2.20 (4 H, ov, 12- and 13-H), 3.42 (3 H, s, OMe), 4.53 (1 H, d, $J_{4\text{-}13}$= 2.3, 4-H), 4.71 (1 H, d, $J_{2\text{-}12}$= 5.9, 2-H), 4.82, 5.03 (each 1 H, each d, J_{gem}=15.5 Hz, CH_2Ph), 6.88 (1 H, dt, $J_{8\text{-}10}$= 1.3, $J_{7\text{-}8}$= $J_{8\text{-}9}$= 6.9 Hz, 8-H), 7.42-7.62 (6 H, ov, Ph and 10-H), 7.52 (1 H, dd, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.91 (1 H, d, $J_{7\text{-}8}$= 6.9 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 30.7, 31.5 (12- and 13-C), 49.1 (*C*H_2Ph), 56.5 (4-C), 60.0 (OMe), 73.8 (2-C), 92.8 (4a-C), 112.1 (8-C), 124.1 (10-C), 127.0, 127.8, 128.1, 138.1 (Ph-C), 127.3 (7-C), 135.3 (9-C), 149.8 (10a-C), 155.0 (11a-C), 155.7 (5-C); mass *m/z* 348 (M^+), 317 (M^+ - OMe). Anal. Found: C, 69.36; H, 5.82; N, 15.93%. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08%.

1-Benzyl-3-benzyloxy-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-5(1*H*)-one (**9b**): yellow oil; IR (NaCl) 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.79-2.19 (4 H, ov, 12- and 13-H) 4.29 (1 H, d, $J_{4\text{-}13}$= 5.0 Hz, 4-H), 4.64 (2 H, s, OCH_2Ph), 4.69 (1 H, d, $J_{2\text{-}12}$= 5.3 Hz, 2-H), 4.72, 4.96 (each 1 H, each d, J_{gem}= 15.5 Hz, NCH_2Ph), 6.81 (1 H, t, $J_{7\text{-}8}$= $J_{8\text{-}9}$= 6.6 Hz, 8-H), 7.16-7.34 (10 H, ov, Ph), 7.35 (1 H, d, $J_{9\text{-}10}$= 8.9 Hz, 10-H), 7.47 (1 H, dd, $J_{8\text{-}9}$= 6.6, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.89 (1 H, d, $J_{7\text{-}8}$= 6.6 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 30.8, 31.6 (12- and 13-C), 49.2 (N*C*H_2Ph), 57.2 (4-C), 74.7 (O*C*H_2Ph), 74.9 (2-C), 93.2 (4a-C), 112.2 (8-C), 124.3 (10-C), 127.1, 127.5, 128.1, 128.3, 138.1, 138.3 (Ph-C), 127.6 (7-C), 135.4 (9-C), 150.0 (10a-C), 155.2 (11a-C), 156.0 (5-C); mass *m/z* 348(M^+). Anal. Found: C, 73.19; H, 5.76; N, 12.89%. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20%.

1-Benzyl-3-methoxy-13-methyl-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-d]pyrimidin-5(1*H*)-one (**9c**): pale yellow prisms from hexane; mp 92-93 °C; IR (KBr) 1655 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.18 (3 H, d, $J_{13\text{-}Me}$= 6.9 Hz, 13-Me), 1.59 (1 H, ddd, $J_{12\text{-}13}$= 3.6, $J_{2\text{-}12}$= 5.3, J_{gem}= 13.2 Hz, 12-H*exo*), 2.13 (1 H, dd, $J_{12\text{-}13}$= 9.6, J_{gem}= 13.2 Hz, 12-H*endo*), 2.34 (1 H, dqd, $J_{12\text{-}13}$= 3.6, $J_{13\text{-}Me}$= 6.9, $J_{12\text{-}13}$= 9.6 Hz, 13-H), 3.41 (3 H, s, OMe), 4.38 (1 H, s, 4-H), 4.56 (1 H, d, $J_{2\text{-}12}$= 5.3 Hz, 2-H), 4.79, 5.03 (each 1 H, each d, J_{gem}= 15.5 Hz, CH_2Ph), 6.85 (1 H, dt, $J_{8\text{-}10}$= 1.3, $J_{7\text{-}8}$= $J_{8\text{-}9}$= 6.9 Hz, 8-H), 7.25-7.41 (6 H, ov, Ph and 10-H), 7.51 (1 H, ddd, $J_{7\text{-}9}$=1.7, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.90 (1 H, dd, $J_{7\text{-}9}$= 1.7, $J_{7\text{-}8}$= 6.9 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 22.2 (13-Me), 39.4, 40.7 (12- and 13-C), 49.2 (*C*H_2Ph), 59.9 (OMe), 62.6 (4-C), 74.9 (2-C), 93.0 (4a-C), 112.3 (8-C), 124.3 (10-C), 127.1, 128.0, 128.3, 138.3 (Ph-C), 127.6 (7-C), 135.3 (9-C), 150.0 (10a-C), 155.1 (11a-C), 155.4 (5-C); mass *m/z* 362(M^+), 331 (M^+ - OMe). Anal. Found: C, 69.74; H, 6.16; N, 15.40%. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6,12; N, 15.46%.

1-Benzyl-3-benzyloxy-13-methyl-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]-pyrimidin-5(1*H*)-one (**9d**): pale yellow oil; IR (NaCl) 1655 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.24 (3 H, d, $J_{13\text{-}Me}$= 6.9 Hz, 13-Me), 1.49 (1 H, ddd, $J_{12\text{-}13}$= 3.6, $J_{2\text{-}12}$= 5.3, Jgem= 13.2 Hz, 12-H*exo*), 2.05 (1 H, dd, $J_{12\text{-}13}$= 9.9, J_{gem}= 13.2 Hz, 12-H*endo*), 2.29 (1 H, m, 13-H), 4.26 (1 H, d, $J_{2\text{-}12}$= 5.3 Hz, 2-H), 4.31 (1 H, s, 4-H), 4.61 (2 H, s, OCH_2Ph), 4.71, 4.96 (each 1 H, each d, J_{gem}= 15.2 Hz, NCH_2Ph), 6.85 (1 H, dt, $J_{8\text{-}10}$= 1.3, $J_{7\text{-}8}$= $J_{8\text{-}9}$= 6.9 Hz, 8-H), 7.16-7.36 (11 H, ov, Ph and 10-H), 7.51 (1 H, ddd, $J_{7\text{-}9}$= 1.7, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.91 (1 H, ddd, $J_{7\text{-}10}$= 0.7, $J_{7\text{-}9}$= 1.7, $J_{7\text{-}8}$= 6.9 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 22.2 (13-Me), 39.3, 40.6 (12- and 13-C), 49.2 (N*C*H_2Ph), 63.1 (4-C), 74.8, 75.6 (O*C*H_2Ph and 2-C), 93.1 (4a-C), 112.3 (8-C), 124.3 (10-C), 127.1, 127.5, 128.0, 128.1, 128.4, 128.7, 138.2, 138.4 (Ph-C), 127.6 (7-C), 135.4 (9-C), 150.0 (10a-C), 155.2 (11a-C), 155.5 (5-C). Found: C, 73.69; H, 6.08; N, 12.62%. Anal. Calcd for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78%.

1-Benzyl-3-methoxy-13-phenyl-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-5(1*H*)-one (**9e**): pale yellow oil; IR (NaCl) 1665 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.09 (1 H, ddd, $J_{12\text{-}13}$= 5.0, $J_{2\text{-}12}$= 5.3, J_{gem}= 13.5 Hz, 12-H*exo*), 2.46 (1 H, dd, $J_{12\text{-}13}$= 10.2, J_{gem}= 13.5 Hz, 12-H*endo*), 3.41 (1 H, dd, $J_{12\text{-}13}$= 5.0, $J_{12\text{-}13}$= 10.2 Hz, 13-H), 3.47 (3 H, s, OMe), 4.71 (1 H, d, $J_{2\text{-}12}$= 5.3 Hz, 2-H), 4.75 (1 H, s, 4-H), 4.83, 5.13 (each 1 H, each d, J_{gem}= 15.5 Hz, CH_2Ph), 6.85 (1 H, dt, $J_{8\text{-}10}$= 1,3, $J_{7\text{-}8}$= $J_{8\text{-}9}$= 5.6 Hz, 8-H), 7.18-7.56 (12 H, ov, Ph and 9- and 10-H), 8.90 (1 H, d, $J_{7\text{-}8}$= 5.6 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 41.5 (12-C), 49.2 (13-C), 50.4 (*C*H_2Ph), 60.3 (OMe), 63.0 (4-C), 74.7 (2-C), 92.8 (4a-C), 112.4 (8-C), 124.4 (10-C), 126.4, 127.1, 127.7, 128.1, 128.4, 138.3, 145.5 (Ph-C), 127.3 (7-C), 135.6 (9-C), 150.2 (10a-C), 155.1 (11a-C), 155.4 (5-C). Anal. Found: C, 73.49; H, 5.90; N, 12.78%. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20%.

1-Benzyl-6,7-dimethyl-3-methoxy-1,2,3,4-tetrahydro-2,4-ethanopyrido[4,5-*d*]pyrimidin-5(6*H*)-one (**10**): yellow oil; IR (NaCl) 1630 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.89-2.12 (4 H, ov, 9- and 10-H), 2.19 (3 H, s, 7-Me), 3.42 (3 H, s, 6-Me), 3.54 (3 H, s, OMe), 4.40 (1 H, d, $J_{4\text{-}10}$= 3.6 Hz, 4-H), 4.48 (2 H, s, CH_2Ph), 4.58 (1 H, d, $J_{2\text{-}9}$= 3.6 Hz, 2-H), 5.60 (1 H, s, 8-H), 7.29-7.34 (5 H, ov, Ph); ^{13}C NMR ($CDCl_3$) δ= 21.2 (7-Me), 30.0 (6-Me), 31.4, 31.7 (9- and 10-C), 53.1 (*C*H_2Ph), 56.2 (OMe), 60.0 (4-C), 75.9 (2-C), 95.2 (8-C), 102.3 (4a-C), 126.3, 127.1, 128.5, 138.2 (Ph-C), 144.3 (7-C), 149.0 (8a-C), 161.5 (5-C). Anal. Found: C, 70.22; H, 7.29; N, 12.77%. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91%.

Azepine-ring Formation of Hydrazone 11. A solution of aldehyde **1a** (0.316 g, 1.00 mmol) and 4-aminomorpholine (**4c**; 0.12 ml, 1.24 mmol) in benzene (8 ml) containing a drop of acetic acid was stirred at room temperature for 18 h. The solvent was removed *in vacuo*. The residue was neutralized with 5% aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 x 20 ml). The combined organic layer was evaporated to dryness. The residue was treated with column chromatography on silica gel with hexane/ethyl acetate (= 1:4) to afford hydrazone **11** (0.346 g, 86%). The toluene solution (5 ml) of **11** (0.0953 g, 0.24 mmol) deoxygenated by flashing argon stream was heated under reflux for 3 h. Usual work-up of the reaction mixture gave azepine **12** (0.0830 g, 87%).

2-(*N*-Allylbenzylamino)-3-(morpholino)iminomethylpyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**11**): yellow oil; IR (NaCl) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 3.05 [4 H, t, *J*= 5.0 Hz, morpholino-H(2,6)], 3.83 [4 H, t, *J*= 5.0 Hz, morpholino-H(3,5)], 4.15 (2 H, d, *J*= 5.9 Hz, NCH_2CH=CH_2), 4.86 (2 H, s, CH_2Ph), 5.12-5.19 (2 H, ov, NCH_2CH=CH_2), 5.84 (1 H, m, NCH_2CH=CH_2), 6.86 (1 H, dd, *J*= 6.3, 8.9 Hz, 7-H), 7.22-7.30 (6 H, ov, Ph and 9-H), 7.58 (1 H, ddd, *J*= 1.7, 6.6, 8.9 Hz, 8-H), 7.89 (1 H, s, -CH=N-), 8.86 (1 H, dd, *J*= 1.7, 6.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$) δ= 52.0, 52.5, 52.6 [*C*H_2Ph and N*C*H_2CH=CH_2 and morpholino-C(2,6)], 66.5 [morpholino-C(3,5)], 93.4 (3-C), 112.7 (7-C), 117.6 (-CH=*C*H_2), 124.5 (9-C), 126.9, 127.5, 128.3, 138.1 (Ph-C), 127.6 (6-C), 134.1, 134.4 (-*C*H=CH_2 and 8-C), 135.9 -CH=N-N<), 147.9 (9a-C), 158.8 (2-C), 159.2 (4-C). Anal. Found: C, 68.18; H, 6.48; N, 17.51%. Calcd for $C_{23}H_{25}N_5O$: C, 68.46; H, 6.25; N, 17.36%.

1-Benzyl-5-morpholinoamino-4,5-dihydoropyrido[1',2':1,2]pyrimido[4,5-*b*]azepin-6(1*H*)-one (**12**): pale yellow prisms from 2-propanol; mp 164-165 °C; IR (KBr) 3200 (NH), 1650 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.35-2.91 [7 H, ov, morpholino-H(2,6) and 4-H and 4-NH], 3.69-3.74 [4 H, ov, morpholino-H(3,5)], 5.05, 5.34 (each 1 H, each d, J_{gem}= 15.5 Hz, CH_2Ph), 5.04 (1 H, dd, $J_{4\text{-}5}$= 3.6, $J_{3\text{-}5}$= 4.0 Hz, 5-H), 5.14 (1 H, ddd, $J_{3\text{-}5}$= 4.0, $J_{3\text{-}4}$=4.3, $J_{2\text{-}3}$= 9.2 Hz, 3-H), 6.08 (1 H, dd, $J_{2\text{-}4}$= 2.6, $J_{2\text{-}3}$= 9.2 Hz, 2-H), 6.87 (1 H, dd, $J_{9\text{-}10}$= 6.6, $J_{8\text{-}9}$= 7.3 Hz, 9-H), 7.21-7.40 (6 H, ov, Ph and 11-H), 7.52 (1 H, ddd, $J_{8\text{-}10}$= 1.7, $J_{9\text{-}10}$= 6.6, $J_{10\text{-}11}$= 8.3 Hz, 10-H), 8.82 (1 H, dd, $J_{8\text{-}10}$= 1.7, $J_{8\text{-}9}$= 7.3 Hz, 8-H); ^{13}C NMR ($CDCl_3$) δ= 29.8 (4-C), 54.6, 55.1 (*C*H_2Ph and 5-C), 57.0 [morpholino-C(2,6)], 67.2 [morpolino-C(3,5)], 99.7 (5a-C), 111.8 (9-C), 113.0 (3-C), 124.8 (11-C), 126.9, 127.4, 128.3, 139.0 (Ph-C), 127.3 (8-C), 131.3 (2-C), 135.5 (10-C),

147.4 (11a-C), 157.6 (12a-C), 158.8 (6-C); mass *m/z* 403 (M^+), 303. Anal. Found: C, 68.61; H, 6.30; N, 17.10%. Calcd for $C_{23}H_{25}N_5O_2$: C, 68.46; H, 6.25; N, 17.36%.

Reaction of Aldehydes 1a, 1b, 2, and 3 with Tosylamide (4d) in the Presence of PTSA. Typical Procedure: A solution of aldehyde **1a** (0.160 g, 0.50 mmol), tosylamide (**4d**; 0.111 g, 0.65 mmol), and 1 crop of PTSA in xylene (5 ml) was deoxygenated by flashing argon stream for 1 h. The mixture was heated under reflux for 6 h. Usual work-up of the reaction mixture and purification with column chromatography on silica gel with hexane/ethyl acetate/chloroform (= 4:1:1) gave ethanopyridopyrimidopyrimidine **13a** (0.210 g, 89%).

Similarly, products **13b**, **14**, and **15** resulting from the ene reaction of the corresponding *N*-tosyl imines were obtained.

1-Benzyl-3-(*p*-toluenesulfonyl)-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]pyrimidin-5(1*H*)-one (**13a**): pale yellow needles from EtOH; mp 210 °C; IR (KBr) 1665 (CO), 1350, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.69-2.39 (4 H, ov, 12- and 13-H), 1.99 (3 H, s, Me), 4.20, 5.30 (each 1 H, each d, J_{gem}= 14.9 Hz, C*H*$_2$Ph), 5.21 (1 H, d, $J_{4\text{-}13}$= 5.6 Hz, 4-H), 5.36 (1 H, d, $J_{2\text{-}12}$= 5.3 Hz, 2-H), 6.86 (2 H, d, $J_{o\text{-}m}$= 7.9 Hz, Ar-H), 6.91 (1 H, dd, $J_{7\text{-}8}$= 5.6, $J_{8\text{-}9}$= 6.9 Hz, 8-H), 7.12 (1 H, d, $J_{9\text{-}10}$= 8.9 Hz, 10-H), 7.29-7.37 (5 H, ov, Ph), 7.52 (2 H, d, $J_{o\text{-}m}$= 7.9 Hz, Ar-H), 7.54 (1H, dd, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 8.9 Hz, 9-H), 8.82 (1 H, d, $J_{7\text{-}8}$= 5.6 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 21.1 (Me), 36.1, 36.3 (12- and 13-C), 50.7 (*C*H$_2$Ph), 55.5 (4-C), 73.8 (2-C), 92.9 (4a-C), 112.6 (8-C), 124.1 (10-C), 127.5, 127.7, 128.3, 128.6, 128.7, 135.1, 137.6, 143.2 (Ph- and Ar-C), 127.8 (7-C), 135.8 (9-C), 149.7 (10a-C), 154.0 (11a-C), 154.3 (5-C); mass *m/z* : 472 (M^+), 408 (M^+ - SO_2), 317 (M^+ - Ts). Anal. Found: C, 66.12; H, 5.17; N, 11.83%. Calcd for $C_{26}H_{24}N_4O_3S$: C, 66.08; H, 5.12; N, 11.86%.

1-Benzyl-13-methyl-3-(*p*-toluenesulfonyl)-3,4-dihydro-2,4-ethano-2*H*-pyrido[1',2':1,2]pyrimido[4,5-*d*]-pyrimidin-5(1*H*)-one (**13b**): pale yellow plates from propan-2-ol; mp 218 °C; IR (KBr) 1670, 1350, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.13 (3 H, d, $J_{13\text{-}Me}$= 6.9 Hz, 13-Me), 1.62 (3 H, s, Me), 1.67 (1 H, ddd, $J_{12\text{-}13}$= 3.3, $J_{2\text{-}12}$= 5.9, J_{gem}= 13.2 Hz, 12-H*exo*), 1.92 (1 H, dd, $J_{12\text{-}13}$= 8.2, J_{gem}= 13.2 Hz, 12-H*endo*), 2.41-2.49 (1 H, m, 13-H), 4.16, 5.32 (each 1 H, each d, J_{gem}= 14.9 Hz, C*H*$_2$Ph), 4.77 (1 H, s, 4-H), 5.36 (1 H, d, $J_{2\text{-}12}$= 5.9 Hz, 2-H), 6.85 (2 H, d, $J_{o\text{-}m}$= 8.3 Hz, Ar-H), 6.90 (1 H, t, $J_{7\text{-}8}$= 6.9 Hz, 8-H), 7.12 (1 H, d, $J_{9\text{-}10}$= 9.9 Hz, 10-H), 7.26-7.36 (5 H, ov, Ph), 7.51 (2 H, d, $J_{o\text{-}m}$= 8.3 Hz, Ar-H), 7.55 (1 H, dd, $J_{8\text{-}9}$= 6.9, $J_{9\text{-}10}$= 9.9 Hz, 9-H), 8.81 (1 H, d, $J_{7\text{-}8}$= 6.9 Hz, 7-H); ^{13}C NMR ($CDCl_3$) δ= 21.1, 21.5 (Me and 13-Me), 44.2, 44.8 (12- and 13-C), 50.6 (*C*H$_2$Ph), 61.1 (4-C), 74.2 (2-C), 92.5 (4a-C), 112.6 (8-C), 124.1 (10-C), 127.5, 127.7, 128.3, 128.6, 128.7, 135.4, 137.7, 143.2 (Ph- and Ar-C), 127.8 (7-C), 135.7 (9-C), 149.6 (10a-C), 153.9 (11a-C), 154.0 (5-C); mass *m/z* 486 (M^+), 331 (M^+ - Ts), 289. Anal. Found: C, 66.77; H, 5.37; N, 11.43%. Calcd for $C_{27}H_{26}N_4O_3S$: C, 66.64; H, 5.39; N, 11.52%.

1-Benzyl-6,7-dimethyl-3-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-2,4-ethanopyrido[4,5-*d*]pyrimidin-5(6*H*)-one (**14**): yellow prisms from benzene and EtOH; mp 167-169 °C; IR (KBr) 1635 (CO), 1340, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.91-2.25 (4 H, ov, 9- and 10-H), 2.08 (3 H, s, 7-Me), 2.32 (3 H, s, Me), 3.38 (3 H, s, 6-Me), 4.32, 4.40 (each 1 H, each d, J_{gem}= 17.5 Hz, C*H*$_2$Ph), 5.11 (1 H, d, $J_{4\text{-}10}$= 4.0 Hz, 4-H), 5.12-5.18 (2 H, ov, 2- and 8-H), 7.09 (2 H, d, $J_{o\text{-}m}$= 8.3 Hz, Ar-H), 7.19-7.38 (5 H, ov, Ph), 7.63 (2 H, d, $J_{o\text{-}m}$= 8.3 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ= 21.1, 21.4 (7-Me, Me), 30.2 (6-Me), 35.8 (10-C), 36.9 (9-C), 54.2 (*C*H$_2$Ph), 55.9 (4-C), 75.1 (2-C), 95.3 (8-C), 103.1 (4a-C), 126.8, 127.6, 128.4, 137.4, 127.7, 128.8, 135.9, 143.0 (Ph- and Ar-C), 144.7 (7-C), 147.8 (8a-C), 160.4 (5-C); mass *m/z* 449 (M^+), 294 (M^+ - Ts). Anal. Found: C, 66.64; H, 6.00; N, 9.34%. Calcd for $C_{25}H_{27}N_3O_3S$: C, 66.79; H, 6.05; N, 9.35%.

1-Benzyl-6,8-dimethyl-3-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydro-2,4-ethanopyrimido[4,5-*d*]pyrimidine-5,7(6*H*,8*H*)-dione (**15**). This product was obtained as colorless prisms from hexane and benzene. This

revealed to be 2:1 molecular complex of **15** and benzene; mp 134-136 °C; IR (KBr) 1640 (CO), 1340, 1155 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.60-2.09 (4 H, ov, 9- and 10-H), 2.43 (3 H, s, Me), 3.33 (3 H, s, 8-Me), 3.37 (3 H, s, 6-Me), 4.12, 4.28 (each 1 H, each d, J_{gem}= 16.2 Hz, CH_2Ph), 5.03-5.08 (2 H, ov, 2- and 4-H),, 7.26 (3 H, s, benzene), 7.30-7.46 (7 H, ov, Ph and Ar-H), 7.71 (2 H, d, $J_{o\text{-}m}$= 7.9 Hz, Ar-H); ^{13}C NMR ($CDCl_3$) δ= 21.6 (Me), 28.0 (8-Me), 30.5 (10-C), 32.7 (6-Me), 36.7 (9-C), 54.9 (CH_2Ph), 55.4 (4-C), 74.7 (2-C), 102.1 (4a-C), 127.3, 127.4, 128.1, 129.1, 129.9, 135.1, 136.6, 144.2 (Ph- and Ar-C), 128.4 (benzene-C), 152.2 (7-C), 152.3 (8a-C), 160.4 (5-C); mass *m/z* 466 (M^+), 375 (M^+ - C_7H_7), 311 (M^+ - Ts). Anal. Found: C, 64.44; H, 5.83; N, 11.13%. Calcd for $C_{24}H_{26}N_4O_4S \cdot 1/2C_6H_6$: C, 64.14; H, 5.78; N, 11.14%.

Kinetic Studies. Typical Procedure: A solution of oxime **5a** in ODCB (0.1 ml) and diglyme (15 ml) was placed in a test tube. The tube was sealed under argon and placed in one neck of a two-necked flask. A condenser was placed on the other neck and the flask was filled with a solvent with appropriate bp, such as triethylamine (bp 88.9 °C), butan-2-ol (bp 99.5 °C), toluene (bp 110.6 °C), butan-1-ol (bp 117.7 °C), chlorobenzene (bp 131.7 °C), acetic anhydride (bp 140.0 °C), and DMF (bp 153.0 °C) until the solvent was just touching the bottom of the test tube. The outer flask was placed in a thermostatic oil bath and heated to keep the solvent refluxing. At appropriate interval an aliquot of the ODCB-diglyme solution (0.05 ml) was withdrawn with a micro syringe through a septum. The collected sample was immediately cooled in an ice-salt bath to stop the reaction and analyzed by HPLC. HPLC measurements were performed with a Hitachi L-6200 instrument using a UV detector (Hitachi L-4000; 254 nm) and Wakopac QID (id 4.6 mm x 250 mm) column. The flow rate of the elution with acetonitrile/water (= 4:6) was 1.0 ml min^{-1}. The rate of the disappearance of oxime **5a** was determined with an integrator (Hitachi D-2500) using ODCB as internal standard. All rates of conversion of **5a** under several conditions (temperature and solvent) were of first-order with respect to the oxime concentrations. The rate constants are summarized as bellows; for oxime **5a**: k x 10^5 (sec^{-1}) (at °C); 1.23 (100), 4.24 (118), and 30.0 (140) in diglyme and 2.98 (118) in pentan-1-ol and 4.43 (118) in DMF. For aldehyde **1a**: k x 10^5 (sec^{-1}) (at °C); 0.658 (118), 2.07 (132), 4.82 (140), and 11.06 (153) in diglyme and 0.575 (118) in pentan-1-ol and 0.258 (118) in DMF. For aldehyde **2** in diglyme: k x 10^5 (sec^{-1}) (at °C); 2.89 (100), 4.53 (108), 5.81 (110), and 10.4 (118). For oxime **6** in diglyme: k x 10^5 (sec^{-1}) (at °C); 2.56 (89), 5.11 (100), 14.7 (111), and 16.1 (118).

The activation parameters of the imine and carbonyl ene reactions are summarized in Table 3.

Computational Procedures. Heats of formation in the reactants and products were calculated as follows; the five lowest conformers were generated MM2 force field using the MacroModel program (Version 3.5a).[16] They were surveyed as initial geometries and fully optimized individually with PM3 method using MOPAC program (Version 6.00). The lowest heat of formation thus obtained each for reactant and product was selected as that of ground state. Locations of transition structures were searched by constructing roughly potential energy surfaces as two reaction coordinates (newly formed C1-C7 and Y8-H9 distance). Transition structures were optimized using the keyword TS and PRECISE implemented in the MOPAC program. The FORCE calculations for the optimized transition structures showed one negative eigenvalue in the Hessian matrix with the correct displacement coordinates, which was further confirmed by the IRC calculations. All these calculations were performed on the VAX 4000 in Ube Laboratory, Corporate Research & Development, Ube Industries. LTD.

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