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Generation of NH-azomethine imine intermediates through the 1,2-hydrogen shift of hydrazones and their intermolecular cycloaddition reaction with olefinic dipolarophiles

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Abstract—The thermal 1,2-hydrogen shift of the hydrazone generates the NH-azomethine imine intermediate in the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde system under mild conditions. Therein, the resulting NH-azomethine imine should be stabilized by forming an internal hydrogen bond with the carbonyl oxygen at the 4-position. Its smooth stereoselective intermolecular cycloaddition reaction with olefinic dipolarophiles giving pyrazolidine derivatives is discussed.

1. Introduction

The concept of the thermal isomerization of hydrazone to NH-azomethine imine through the 1,2-hydrogen shift was proposed by Grigg and co-workers in 1978[1] earlier than that of oxime–nitrone.[2] However, few reports[3] on further investigations concerning the synthetic and mechanistic aspects have been accomplished in comparison with those on acid-catalyzed hydrazone–azomethine imine isomerization,[4] or on the thermal oxime–nitrone one.[5] As a reason, the pyrazolidines obtained from NH-azomethine imines and olefinic dipolarophiles were not very stable and dehydrogenated to 2-pyrazoline derivatives under reaction conditions and/or purification procedures. This provided an ambiguity of the mechanism and stereochemistry of the 1,3-dipolar cycloaddition process. As a part of our project to develop 1,3-dipolar cycloaddition reactions at the periphery of heterocyclic system, we reported that facile thermal isomerizations of the oxime and hydrazone to the NH-nitrone and -azomethine imine took place under neutral conditions. The intramolecular cycloaddition reaction of the dipoles with olefinic dipolarophiles provided isoxazolidine and pyrazolidine derivatives fused by heterocycles, respectively.[6] Therein, we proposed that the 1,2-hydrogen shift was assisted by the functional groups, e.g. carbonyl and/or amino ones, occupied at the proper positions in the same molecule and that the resulting NH-nitrone and -azomethine imine should be stabilized by forming the internal hydrogen bond with the carbonyl oxygen (Scheme 1).

In order to obtain further information on the isomerization process, we examined the thermal reaction of 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazones with olefinic dipolarophiles. We describe here that the hydrogen bond formation between the resulting NH-azomethine imine and the carbonyl oxygen at the 4-position should be requisite for the facile thermal isomerization. Also, the synthetic utility of the intermolecular cycloaddition reaction of the resulting NH-azomethine imine with olefinic electron-deficient dipolarophiles will be discussed.

2. Results and discussion

2.1. Thermal reaction of 2-substituted 4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazones with olefinic dipolarophiles

In order to elucidate the scope and features of the hydrazone–azomethine imine isomerization in pyrido[1,2-*a*]pyrimidin-4(4*H*)-one system, five phenyl hydrazones **3a**–**e** were prepared and explored the thermal reaction with olefinic dipolarophiles (Scheme 2).

Reaction of hydrazone **3a** with *N*-phenylmaleimide (**6**) in refluxing ethanol (EtOH) gave the desired NH-azomethine imine cycloadduct **7a**, dehydrogenated product **8a**, 2-(pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**9a**), and 2-pyrazoline **10** in 69%, trace, 27, and 30% yields, respectively. The structures of **7a**, **8a**, and **10** were fully

Keywords: hydrazone; NH-azomethine imine; thermal 1,2-H shift; cycloaddition; pyrazolidine.

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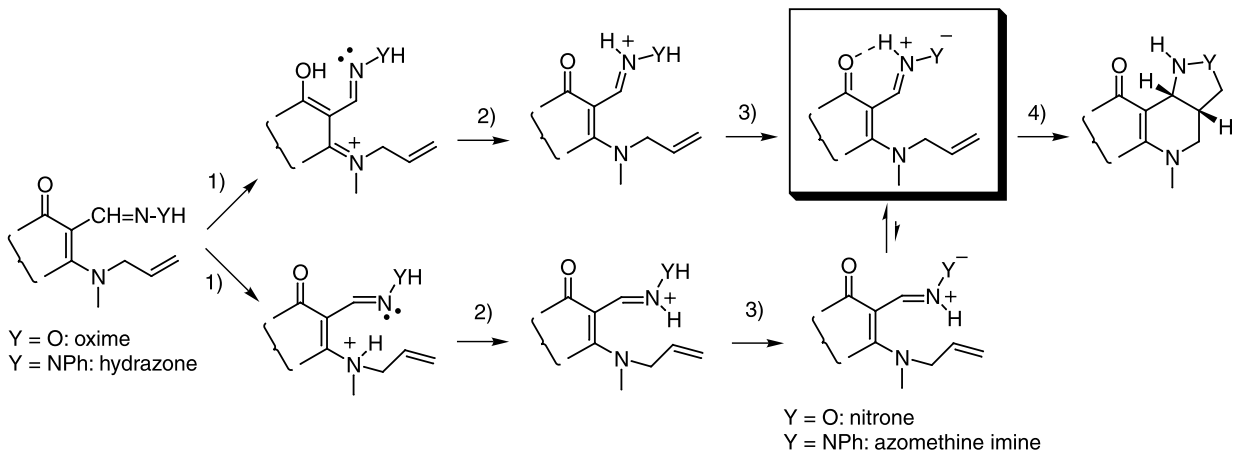
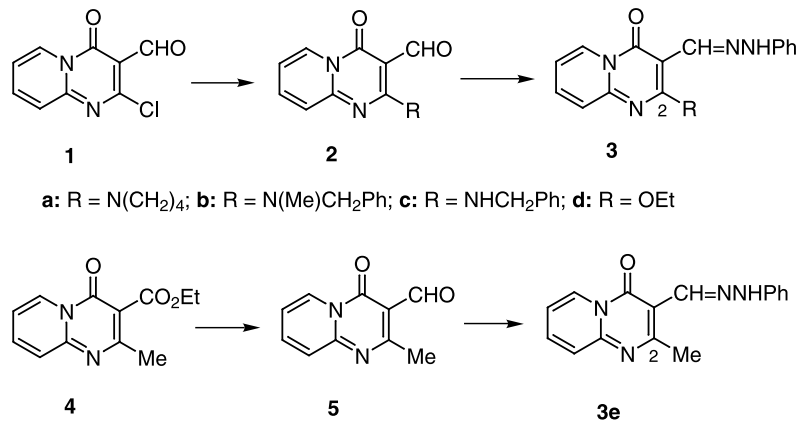


Scheme 1. *Reactions*. (1) Protonation; (2) proton transfer to the imino nitrogen; (3) deprotonation; (4) *endo*-cycloaddition.



Scheme 2.

characterized by COSY and/or NOE experiments as well as the coupling constants; for example, the relative configurations among the three methine protons (Ha, Hb, and Hc) in **7a** were assigned to be all *cis* on the basis of the NOE results and the coupling constants demonstrated in Figure 1. This means that the cycloaddition reaction proceeded in an *endo*-approaching manner of maleimide **6** to the NH-azomethine imine intermediate. Cycloadduct **7a** was not very stable and converted partially to **8a** on long standing under air or on treating with a column chromatography on silica gel. Although the reaction path to **9a** and **10** will be discussed in a later section, these are secondary products from cycloadduct **7a** (Scheme 3).

To obtain further information of the reaction features, the reaction of **3a** with **6** at room temperature for 5 days gave **7a** (86%) and **8a** (5%) together with trace amounts of **9a** and **10**. It should be noted that the hydrazone–azomethine imine isomerization of **3a** took place at room temperature. Similar reactions in acetonitrile and benzene at reflux were also examined; in both cases the four products **7a**, **8a**, **9a**, and **10** were formed in excellent total yields, but the product ratios were substantially different (Table 1; entries 3 and 4). The formation of secondary products **9a** and **10** was suppressed perfectly by addition of 0.25 equiv. of triethylamine (entry 5).

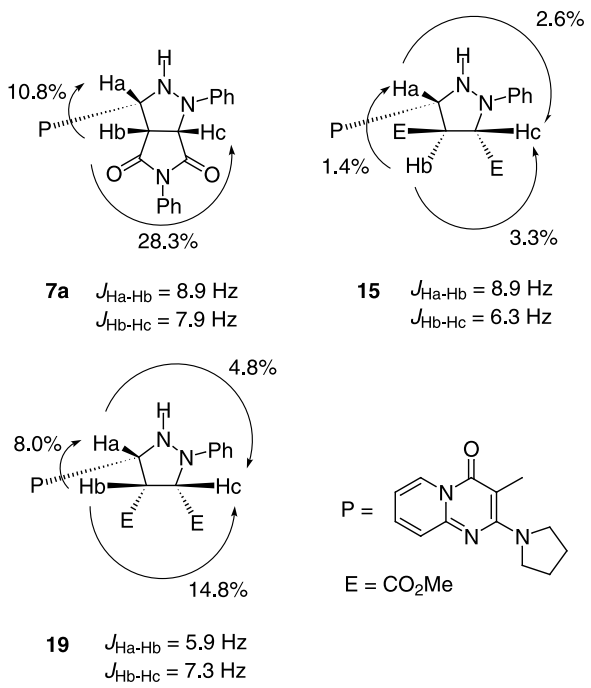
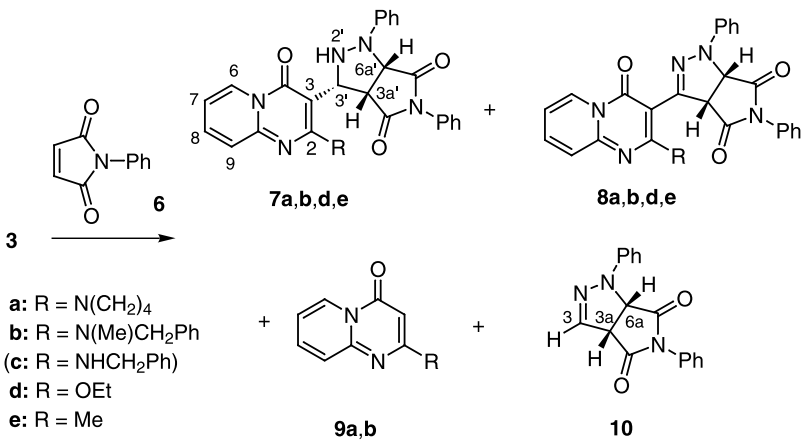


Figure 1. Selected NOE signal enhancements and coupling constants among the pyrazolidine-ring protons.



Scheme 3.

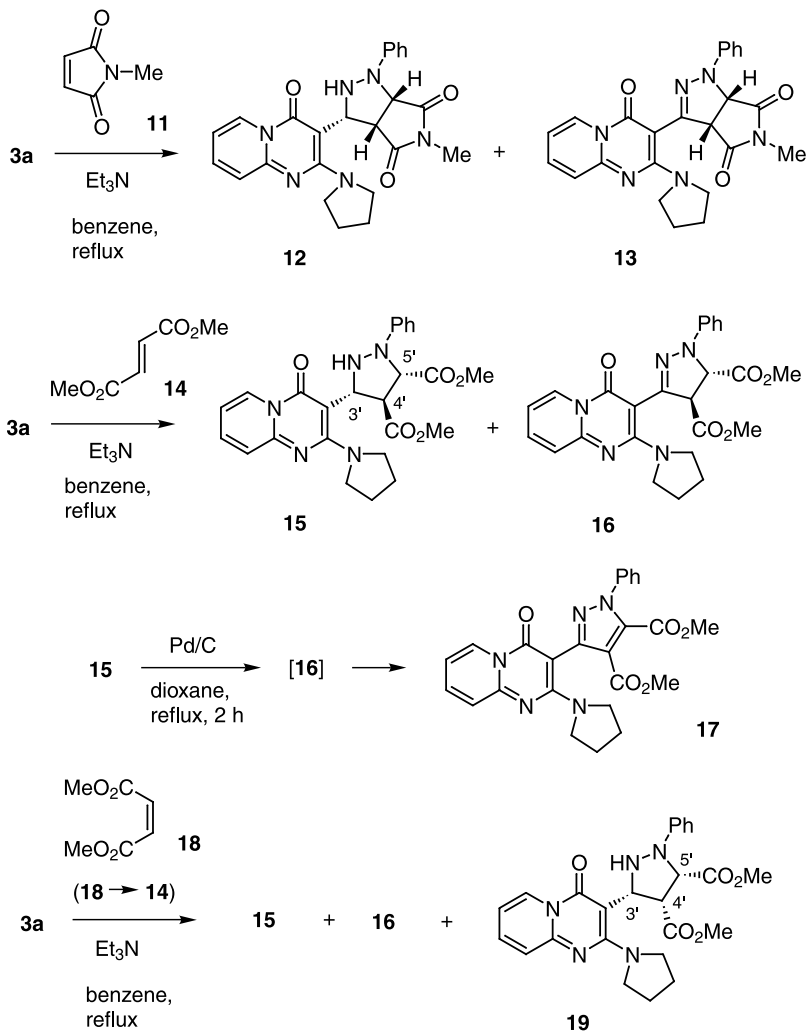
Table 1. Thermal reaction of hydrazone **3** with olefinic dipolarophiles **6**, **11**, **14**, and **18**

Entry	Hydrazone	Dipolarophile	Conditions	Et_3N (equiv.)	Products (yield, %)	Recovered **3**
1	**3a**	**6**	EtOH, reflux, 20 h	None	**7a** (69), **8a** (trace), **9a** (27), **10** (30)	
2	**3a**	**6**	EtOH, room temperature, 5 d	None	**7a** (86), **8a** (5), **9a** (trace), **10** (trace)	
3	**3a**	**6**	Benzene, reflux, 20 h	None	**7a** (48), **8a** (32), **9a** (17), **10** (10)	
4	**3a**	**6**	MeCN, reflux, 20 h	None	**7a** (72), **8a** (trace), **9a** (23), **10** (26)	
5	**3a**	**6**	Benzene, reflux, 20 h	0.25	**7a** (87), **8a** (13)	
6	**3b**	**6**	EtOH, reflux, 20 h	None	**7b** (73), **8b** (8), **9b** (17), **10** (14)	
7	**3b**	**6**	Benzene, reflux, 20 h	0.25	**7b** (91), **8b** (9)	
8	**3d**	**6**	EtOH, reflux, 4 h	None	**7d** (82), **8d** (12)	
9	**3e**	**6**	EtOH, reflux, 48 h	None	*endo*-**7e** (50), **8e** (trace)	**3e** (22)
10	**3e**	**6**	Benzene, reflux, 30 h	None	*endo*-**7e** (60), *exo*-**7e′** (10), **8e** (9)	**3e** (15)
11	**3e**	**6**	1,2-DCE, reflux, 30 h	None	*endo*-**7e** (74), *exo*-**7e′** (14), **8e** (5)	
12	**3a**	**11**	Benzene, reflux, 20 h	0.25	**12** (82), **13** (12)	
13	**3a**	**14**	Benzene, reflux, 3 d	0.25	**15** (45), **16** (29)	**3a** (17)
14	**3a**	**18**	Benzene, reflux, 3 d	0.25	**15** (34), **16** (trace), **19** (28)	**3a** (22)

2-Amino-substituted hydrazones **3b** and **3c**, 2-ethoxy-substituted **3d**, and 2-methyl-substituted **3e** were allowed to react with **6** in aprotic and protic solvents with and/or without triethylamine. The thermal reaction of **3b** with **6** in EtOH gave **7b**, **8b**, **9b**, and **10** in an excellent total yield, while a similar reaction in benzene in the presence of triethylamine (0.25 equiv.) gave **7b** and **8b** in a quantitative total yield. A similar thermal reaction of **3d** with **6** in EtOH in the presence of triethylamine also gave **7d** and **8d**. The reaction of **3e** with **6** in EtOH and benzene at reflux for 48 h gave an inseparable mixture of diastereomers *endo*-**7e** and *exo*-**7e′** (see Section 4) in moderate yields together with the recovered hydrazone **3e** probably due to the poor solubility of **3e** in these solvents. To solve this problem, the reaction of **3e** with **6** in dichloroethane (1,2-DCE) at reflux for 28 h gave *endo*-**7e**, *exo*-**7e′**, and **8e** in 74, 14, and 5% yields, respectively. On the other hand, hydrazone **3c** (*E*-isomer) did not take place the conversion to the NH-azomethine imine in EtOH, butan-1-ol (*n*-BuOH), and toluene at reflux. The hydrazone **3c** was recovered quantitatively and existed as a mixture of *E*/*Z* isomers.

To elucidate the scope and limitations of this isomerization of hydrazones **3** and the cycloaddition reaction of the azomethine imine, the thermal reaction of **3a** with **6** and other dipolarophiles in benzene in the presence of triethylamine (0.25 equiv.) was also examined; the reaction with **6** gave **7a** and **8a** and the reaction with *N*-methylmaleimide (**11**) gave also cycloadduct **12** and dehydrogenated **13**. In the thermal reaction with dimethyl fumarate (**14**) for 3 days, cycloadduct **15** and dehydrogenated **16** (see Section 4) were formed together with the recovered hydrazone **3a**. A similar reaction with dimethyl maleate (**18**) gave three products **15** (34%), **16** (trace), and **19** (28%) and the recovered hydrazone **3a** (22%). This suggested that under the reaction conditions maleate **18** was isomerized into fumarate **14**,[7] both of which reacted with the resulting NH-azomethine imine. Finally, the reaction with ethyl acrylate (**20**) in refluxing benzene for 5 days was examined; hydrazone **3a** was consumed out, but an inseparable mixture of products probably containing regio- and stereo-isomeric cycloadducts was obtained. The assignment of the stereochemistries of the cycloadducts **15** and **19** was also shown in Figure 1. The results of the isomerization of hydrazones **3** and cycloaddition with diporaophiles are summarized in Table 1 (Scheme 4).

The thermal isomerization of hydrazones **3** to the NH-azomethine imine intermediates took place under mild conditions and the intermolecular cycloaddition reaction of the resulting NH-azomethine imines with olefinic dipolarophile proceeded in a stereoselective manner to give pyrazolidine derivatives in good yields. Since the isomerization of 2-ethoxy- **3d** and 2-methyl-substituted



Scheme 4.

hydrazones **3e** also took place under similar mild conditions, the facile generation of NH-azomethine imines in this system should require the existence of carbonyl group at the 4-position. The carbonyl oxygen is possible to form an internal hydrogen bond with the NH of the resulting azomethine imine, which stabilizes the azomethine imine and leans the equilibrium between hydrazone and NH-azomethine imine toward the 1,3-dipole side.

2.2. Reaction of 2-(pyrrolidin-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazones with olefinic dipolarophiles under acidic conditions

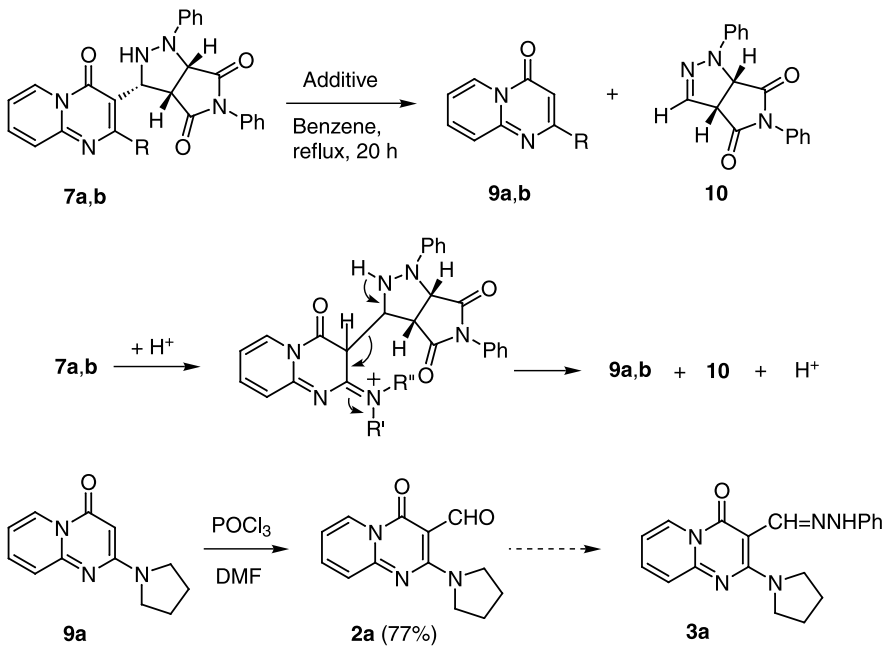
As shortly mentioned above, the reaction of NH-azomethine imine cycloadduct **7a** with basic and acidic reagents was examined to elucidate the reaction path leading to **9a** and **10**. Heating **7a** in benzene with or without 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU; 1.0 equiv.) gave no change and **7a** was recovered in high yields. On the other hand, a solution of **7a** and pyridinium *p*-toluenesulfonate (PPTS; 1.0 equiv.) in benzene was heated at reflux for 20 h to give **9a** and **10** in both 90% yields. The amount of PPTS required for the fission reaction of **7a** was also explored; in the presence of 5 mol% of PPTS, **7a** gave **9a** and **10** in 63 and 60% yields, respectively, together with the recovered **7a** (33%) (Table 2).

A similar fission reaction of cycloadduct **7b** into **9b** and **10** was observed. On the other hand, cycloadducts **7d** and **7e** did not exhibit any change under similar acidic conditions (Scheme 3). Although details are still unclear, a reaction path similar to a retro-Michael type addition process catalyzed by proton is proposed for the fission reaction of[7a,b] (Scheme 5).

Table 2. Fission reaction of cycloadducts **7** in the presence of additives

Entry[a]	Adduct **7**	Additive (equiv.)	Products (yield, %)	Recovered **7**
1	**7a**	None	–	**7a** (100)
2	**7a**	DBU (1.0)	–	**7a** (100)
3	**7a**	PTTS (1.0)	**9a** (90), **10** (90)	–
4	**7a**	PTTS (0.2)	**9a** (77), **10** (67)	**7a** (22)
5	**7a**	PTTS (0.05)	**9a** (63), **10** (60)	**7a** (33)
6	**7b**	PTTS (1.0)	**9b** (90), **10** (93)	–
7	**7d**	PTTS (1.0)	–	**7d** (100)
8	**7e**	PTTS (1.0)	–	**7e** (100)

[a] Reaction conditions: benzene, reflux, 20 h.

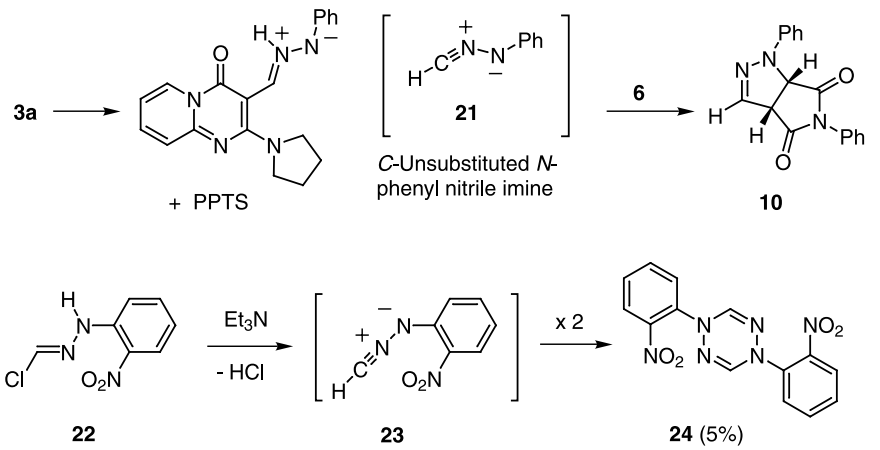


Scheme 5.

Pyrrolidinylpyridopyrimidine **9a** was also converted into the starting aldehyde **2a** in 77% yield by the reaction with Vilsmeier reagent.

The fission product **10** corresponds to the cycloadduct of maleimide **6** with *C*-unsubstituted *N*-phenyl nitrile imine intermediate **21**, which was formed by photolysis of 2-phenyltetrazole and characterized by the spectroscopic properties.[8] However, it has not been applied to organic synthesis except for a few example[9] to our best knowledge. Buzykin et al.[9b] reported that a *C*-unsubstituted nitrile imine **23**, generated from imidoyl chloride **22** and triethylamine, performed a dimerization to give tetrazine **24** in only 5% yield (Scheme 6). However, further intermolecular cycloaddition of **21** with dipolarophiles have not been well documented. Therefore, our next concern was focused on the reaction of **3a** with olefinic dipolarophiles under the acidic conditions.

The reaction of **3a** with maleimide **6** in refluxing benzene in the presence of PPTS (1.0 equiv.) gave **9a** and **10** in 90% yield and quantitatively, respectively. Similar good results were obtained in the reaction with maleimide **11**; the desired **25** and **9a** were formed in 80 and 84% yields, respectively. 2-Pyrazoline **26**, pyrazole **27**, and **9a** were obtained in 51, 28, and 75% yields, respectively, in a similar reaction of **3a** with fumarate **14**. Reducing the amount of PPTS utilized to 0.2 equiv. in the above reaction provided an essentially same results; the yield of aromatized product **27** was decreased, while that of 2-pyrazoline **26** was improved. Unfortunately, the reaction with maleate **18** under similar conditions gave 2-pyrazoline **26**, **27** and **5a**, which were also formed by reaction of **3a** and fumarate **14**. As mentioned above, the reaction with acrylate **20** in the presence of triethylamine gave an inseparable mixture of many products. The reaction with **20** in the presence of PPTS (0.2 equiv.) gave simplified results; two regioisomeric 2-pyrazolines **28** and **29**, pyrazole **30**, and **9a** were obtained in 52, 16, 14 and 82% yields, respectively (Table 3, Scheme 7).

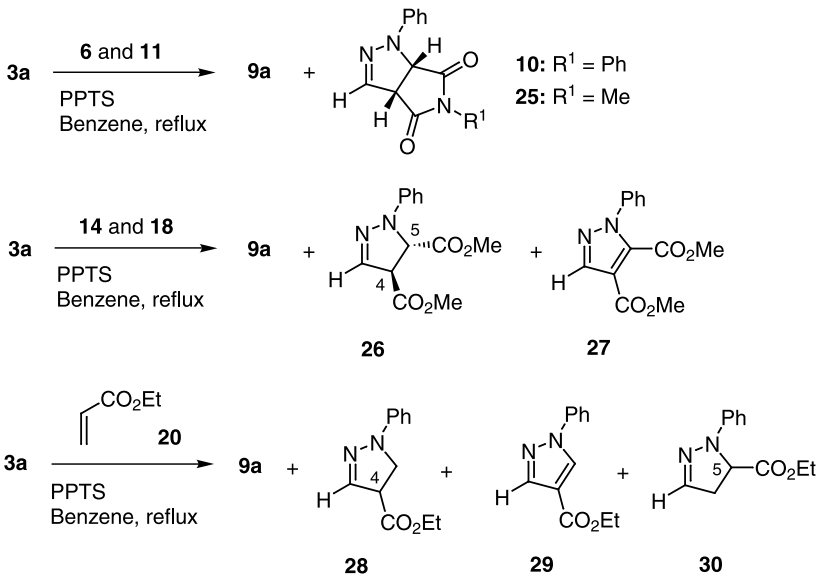


Scheme 6.

Table 3. Reaction of hydrazone **3a** with dipolarophiles **6**, **11**, **14**, **18**, and **20** in the presence of PPTS

Entry[a]	Dipolarophile (equiv.)	PPTS (equiv.)	Time	Products (yield, %)
1	**6** (1.0)	1.0	20 h	**9a** (100), **10** (90)
2	**11** (1.0)	1.0	20 h	**9a** (84), **25** (80)
3	**14** (1.0)	1.0	3 d	**9a** (75), **26** (51), **27** (28)
4	**14** (1.0)	0.2	3 d	**9a** (85), **26** (64), **27** (15)
5	**18** (1.5)	1.0	3 d	**9a** (65), **26** (59), **27** (7)
6	**20** (3.0)	0.2	2 d	**9a** (82), **28** (52), **29** (14), **30** (16)

[a] Reaction conditions: benzene, reflux.



Scheme 7.

It was generally known that acid catalysts accelerated the isomerization of hydrazone to azomethine imine.[4] The intervention of a protonated NH-azomethine imine species was postulated, when strong protic acids such as conc. hydrochloric acid, sulfuric acid, and *p*-toluenesulfonic acid were used as catalysts. In the present case, the PPTS is a weak acid and a catalytic amount of PPTS is effective for the formation of fission products (entries 4 and 6). Thus, we suggest that the intermediates in these reactions under both neutral and acidic conditions are not protonated but ordinary NH-azomethine imines and that the PPTS facilitates the hydrazone–azomethine imine isomerization[3b] as well as the fission reaction of the NH-azomethine imine cycloadducts from hydrazones **3a** and **3b**, which afforded 3-unsubstituted 2-pyrazoline derivatives and 2-(substituted amino)-pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**5a**,**b**).

3. Conclusion

We have reported a facile isomerization of hydrazone to azomethine imine under extremely mild conditions, e.g. at room temperature, in this system, in which the resulting NH-azomethine imine should be stabilized by forming an internal hydrogen bond. Further investigations on the related chemistry are under progress and the results will be reported elsewhere.

4. Experimental

4.1. General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IR Report-100 spectrophotometer from samples as pellets or NaCl discs. ^{1}H NMR spectra were measured on JEOL EX-270 and/or EX-400 spectrometers (270 and 400 MHz, respectively) and ^{13}C NMR spectra were measured on a JEOL EX-270 spectrometer (67.8 MHz) in deuterated-chloroform ($CDCl_3$) solutions unless otherwise stated. Tetramethylsilane was used as internal standard, and *J* values are given in Hz. Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet, m, mutiplet; br, broad signal; and ov, overlapping signals. Mass spectra were determined on a JEOL JMS-SX102A spectrometer. Elemental analyses were performed on a Yanagimoto MT-5 CHN analyzer. All non-aqueous reactions were run under positive pressure of argon or nitrogen. All solvents were dried by standard methods before use. The progress of reactions was monitored by TLC (silica gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (100–200 mesh, Wako Pure Chemical Industries) and/or silica gel 60 (230–400 mesh, Merck).

4.2. Preparation of starting materials

4.2.1. General procedures for the preparation of 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehydes 2. A solution of 2-chloro-4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carbaldehyde (**1**)[10] (5.2 g, 25 mmol), pyrrolidine (2.7 g, 38 mmol) and triethylamine (6.9 mL, 50 mmol) in THF (25 mL) was stirred at room temperature for 3 h. The solvent was evaporated to dryness, which was extracted with dichloromethane (CH_2Cl_2)/5% aqueous sodium hydrogencarbonate. The organic layer was dried on anhydrous magnesium sulfate and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel with ethyl acetate (EtOAc) as an eluent to afford 2-(pyrrolidin-1-yl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**2a**: 4.4 g, 73%). Aldehyde **2a** was used for the next procedure without further purification.

4.2.2. 4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (2a). ^{1}H NMR ($CDCl_3$): 1.95 (4H, br t, J=6.8 Hz, $N(CH_2CH_2)_2$), 3.4–3.8 (4H, br, $N(CH_2CH_2)_2$), 6.38 (1H, td, J=7.0, 1.7 Hz, 7-H), 7.21 (1H, d, J=8.9 Hz, 9-H), 7.62 (1H, m, 8-H), 8.81 (1H, dd, J=7.0, 1.0 Hz, 6-H), 10.27 (1H, s, CHO).

4.2.3. 2-(*N*-Benzylmethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (2b). Yield 85%. ^{1}H NMR ($CDCl_3$): 3.02 (3H, s, NCH_3), 5.30 (2H, s, NCH_2Ph), 6.88 (1H, m, 7-H), 7.20–7.36 (6H, ov, 9-H and Ph-H), 7.65 (1H, m, 8-H), 8.70 (1H, m, 6-H), 10.27 (1H, s, CHO).

4.2.4. 2-(*N*-Benzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (2c). Yield 75%. ^{1}H NMR ($CDCl_3$): 4.84 (2H, m, NCH_2Ph), 6.90 (1H, m, 7-H), 7.27 (6H, ov, 9-H and Ph-H), 7.57, 7.70 (total 1H, each m, 8-H), 9.04, 10.30 (total 1H, s, CHO), 10.02, 11.21 (total 1H, br, NH).

4.2.5. 2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (2d). A solution of sodium ethoxide, prepared from 0.20 g (8.7 mmol) of sodium metal and dry EtOH (20 mL), and aldehyde (**1**: 1.04 g, 5.0 mmol) was stirred at room temperature for 22 h. After similar evaporation and extraction, the residue was subjected to a column chromatography on silica gel with chloroform/methanol (MeOH) (1/1) to afford the desired aldehyde (**2d**: 0.42 g, 39%).

4.2.6. 2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (2d). ^{1}H NMR ($CDCl_3$): 1.48 (3H, t, J=7.2 Hz, OCH_2CH_3), 4.63 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.23 (1H, m, 7-H), 7.54 (1H, d, J=4.5 Hz, 9-H), 7.92 (1H, m, 8-H), 9.17 (1H, m, 6-H), 10.39 (1H, s, CHO).

4.2.7. 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (5). To a solution cooled at −50°C of ethyl 2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**4**:[11] 2.32 g, 10.0 mmol) in CH_2Cl_2 (50 mL) diisobutylaluminium hydride (20 mL of 1.0 M toluene solution, 20.0 mmol) was added slowly. The reaction mixture was stirred for additional 2 h at the same temperature and MeOH (1 mL) was added and the resulting mixture was warmed to room temperature. The reaction mixture was poured into saturated 1 M aqueous Rochelle salt solution (20 mL) and stirred for 1 h. After extraction and evaporation, the residue was subjected to a column chromatography on silica gel with EtOAc and EtOAc/MeOH (5/1) as eluents to afford the desired aldehyde (**5**: 0.86 g, 46%) and alcohol (0.24 g, 12%), respectively.

4.2.8. 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (5). ^{1}H NMR ($CDCl_3$): 2.83 (3H, s, 2-CH_3), 7.33 (1H, m, 7-H), 7.71 (1H, d, J=8.9 Hz, 9-H), 7.99 (1H, m, 8-H), 10.59 (1H, s, CHO).

4.3. General procedures for the preparation of 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carbaldehyde phenyl hydrazones 3

A solution of aldehyde (**2a**: 2.52 g, 10.4 mmol) and phenyl hydrazine (1.23 g, 11.4 mmol) in MeOH (15 mL) was stirred at room temperature for 12 h. The desired hydrazone **3a** (3.19 g, 92%) was obtained as precipitates from the MeOH solution and collected by filtration.

4.3.1. 4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazone (3a). Yellow needles from hexane/EtOAc mp 159–160°C; IR (KBr): 3220 (NH), 1650 (C=O); ^{1}H NMR ($CDCl_3$): 1.85–1.94 (4H, m, $N(CH_2CH_2)_2$), 3.56–3.61 (4H, m, $N(CH_2CH_2)_2$), 6.81 (2H, ov, 7-H and Ph-H), 6.97 (2H, d, J=7.6 Hz, Ph-H), 7.19–7.27 (3H, ov, 9-H and Ph-H), 7.47–7.54 (1H, m, 8-H), 8.05 (1H, br, NH), 8.35 (1H, s, CH=N), 8.85 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 26.1, 51.4, 91.5, 112.5, 112.8, 119.5, 124.7, 127.7, 129.7, 135.8, 136.2, 145.8, 148.5, 156.8, 159.5. Anal. calcd for $C_{19}H_{19}N_5O$ (333.4): C, 68.45; H, 5.74; N, 21.01. Found: C, 68.34; H, 5.69; N, 20.88.

4.3.2. 2-(*N*-Benzylmethylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazone (3b). Yield 96%. Orange crystals from hexane/EtOAc; mp 186–188°C; IR (KBr): 3240 (NH), 1590 (CO); ^{1}H NMR ($CDCl_3$): 2.95 (3H, s, NCH_3), 5.05 (2H, s, NCH_2Ph), 6.76–6.91 (4H, ov, 7-H and Ph-H), 7.16–7.42 (8H, ov, 9-H and Ph-H), 7.51–7.57 (1H, m, 8-H), 7.77 (1H, br, NH), 8.34 (1H, s, CH=N), 8.85 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 41.3, 55.0, 91.8, 112.4, 112.6, 119.1, 124.4, 127.2, 127.4, 128.0, 128.6, 129.2, 135.0, 136.0, 138.0, 145.2, 147.7, 158.8, 159.6. Anal. calcd for $C_{23}H_{21}N_5O$ (383.5): C, 72.04; H, 5.52; N, 18.26. Found: C, 72.10; H, 5.51; N, 18.20.

4.3.3. 2-(*N*-Benzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazone (3c). Y. 77%. Yellow crystals from hexane/EtOAc; mp 216–218°C; IR (KBr): 3240 (NH), 1630 (CO); ^{1}H NMR ($CDCl_3$): 4.86 (2H, d, J=5.0 Hz, NCH_2Ph), 6.60 (1H, m, Ph-H), 6.76, 6.90 (total 1H, m, 7-H), 7.06 (1H, m, Ph-H), 7.32–7.69 (10H, ov, 8-H, 9-H and Ph-H), 8.48 (1H, s, CH=N), 8.93 (1H, m, 6-H), 9.37 (1H, br, NH); ^{13}C NMR ($CDCl_3$): 45.6, 90.2, 112.0, 112.8, 119.3, 124.4, 127.5, 127.6, 128.5, 128.8, 129.2, 136.4, 137.1, 138.4, 144.5, 149.8, 157.0, 157.3. Anal. calcd for $C_{22}H_{19}N_5O$ (369.4): C, 71.53; H, 5.18; N, 18.96. Found: C, 71.60; H, 5.21; N, 18.88.

4.3.4. 2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazone (3d). Yield 87%. Orange crystals from hexane/EtOAc; mp 184–186°C; IR (KBr): 3230 (NH), 1680, 1670 (CO); ^{1}H NMR ($CDCl_3$): 1.55 (3H, t, J=7.3 Hz, OCH_2CH_3), 4.62 (2H, q, J=7.3 Hz, OCH_2CH_3), 6.83 (1H, br t, J=7.3 Hz, 8-H), 7.11–7.16 (3H, ov, Ph-H), 7.24–7.29 (2H, m, Ph-H), 7.50 (1H, m, 9-H), 7.63 (1H, br, NH), 7.74 (1H, m, 7-H), 8.15 (1H, s, CH=N), 9.13 (1H, br d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 14.7, 63.2, 95.1, 112.6, 115.0, 119.5, 124.9, 128.0, 129.1, 132.1, 136.7, 145.1, 148.4, 157.1, 164.2. Anal. calcd for $C_{17}H_{16}N_4O_2$ (308.3): C, 66.22; H, 5.23; N, 18.17. Found: C, 66.29; H, 5.23; N, 18.12.

4.3.5. 2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde phenyl hydrazone (3e). Yield 82%. Orange crystals from hexane/EtOAc; mp 184–186°C; IR (KBr): 3240 (NH), 1680 (CO); ^{1}H NMR ($CDCl_3$): 2.95 (3H, s, 2-CH_3), 6.88 (1H, m, 7-H), 7.05–7.28 (3H, ov, Ph-H), 7.29–7.36 (2H, m, Ph-H), 7.74 (1H, m, 8-H), 7.81 (1H, m, Ph-H), 8.15 (1H, s, CH=N), 9.20 (1H, br d, J=6.9 Hz, 6-H). Anal. calcd for $C_{16}H_{14}N_4O_2$ (278.3): calcd C, 69.03; H, 5.07; N, 20.13. Found: C, 69.16; H, 5.10; N, 20.28.

4.4. General procedures for the reaction of hydrazone 3 with dipolarophiles

A solution of hydrazone **3a** (0.20 g, 0.60 mmol) and maleimide **6** (0.10 g, 0.60 mmol) in EtOH was heated at reflux for 20 h. After cooling, the precipitates **7a** (0.21 g, 69%) was filtered off and the filtrate was evaporated to dryness. The residue was subjected to a column chromatography on silica gel with hexane/EtOAc (6/1), (1/1) and (1/2) as eluents to afford 2-pyrazoline **10** (0.050 g, 30%), dehydrogenated **8a** (trace) and pyridopyrimidine **9a** (0.040 g, 27%), respectively.

4.4.1. NH-Azomethine imine cycloadduct 7a. Yellow crystals without recrystallization; mp 217–218°C; IR (KBr): 3240 (NH), 1775, 1710, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$): 1.91 (4H, br, $N(CH_2CH_2)_2$), 3.71 (5H, ov, $N(CH_2CH_2)_2$ and 3a′-H), 4.70 (1H, dd, J=12.2, 8.9 Hz, 3′-H), 5.02 (1H, d, J=7.9 Hz, 6a′-H), 6.51 (1H, d, J=12.2 Hz, exchangeable with D_2O, 2′-NH), 6.82 (1H, m, 7-H), 6.92 (1H, m, Ph-H), 7.25–7.57 (11H, ov, Ph-H, 8-H and 9-H), 8.73 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 26.1, 50.9, 52.2, 61.6, 71.0, 87.0, 113.2, 115.0, 120.9, 124.8, 127.3, 127.4, 127.5, 128.9, 129.0, 129.4, 129.6, 133.0, 136.7, 148.9, 151.5, 159.1, 161.6, 174.3, 175.6. Anal. calcd for $C_{29}H_{26}N_6O_3$ (506.6): C, 68.76; H, 5.17; N, 16.59. Found: C, 68.62; H, 5.17; N, 16.40.

4.4.2. Dehydrogenated product 8a. Yellow crystals from MeOH; mp 280–281°C; IR (KBr): 1770, 1710, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$): 1.74–1.84 (2H, br, $N(CH_2CHH)_2$), 1.95–1.96 (2H, br, $N(CH_2CHH)_2$) 3.22 (2H, br, $N(CHHCH_2)_2$), 3.58–3.68 (2H, br, $N(CHHCH_2)_2$), 5.23 (1H, d, J=11.2 Hz, 3a′-H), 6.06 (1H, d, J=11.2 Hz, 6a′-H), 6.84 (1H, m, 7-H), 6.97 (1H, t, J=7.6 Hz, Ph-H), 7.23–7.59 (11H, ov, Ph-H, 8-H and 9-H), 8.83 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 25.5, 50.4, 56.0, 65.3, 86.4, 112.7, 115.0, 121.6, 124.7, 126.6, 127.7, 129.3, 129.5, 129.6, 131.9, 136.9, 142.5, 145.7, 149.4, 158.0, 158.7, 172.1, 173.5. Anal. calcd for $C_{29}H_{24}N_6O_3$ (504.6): C, 69.04; H, 4.79; N, 16.66. Found: C, 69.16; H, 4.87; N, 16.58.

4.4.3. 2-(Pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (9a). Although this compound is known in the literature,[12] none of physical and spectroscopic data were found therein. Colorless needles from hexane/benzene; IR (KBr): 1650 (CO); ^{1}H NMR ($CDCl_3$): 1.98 (4H, br, $N(CH_2CH_2)_2$), 3.50 (4H, br, $N(CH_2CH_2)_2$), 5.37 (1H, s, 3-H), 6.80 (1H, m, 7-H), 7.26 (1H, m, 9-H), 7.52 (1H, m, 8-H), 8.87 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 24.6, 46.4, 80.7, 111.7, 124.0, 127.5, 135.9, 150.5, 157.7, 159.0. Anal. calcd for $C_{12}H_{13}N_3O$ (215.3): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.88; H, 6.13; N, 19.40.

4.4.4. 2-Pyrazoline 10. Colorless needles from hexane/EtOAc; mp 158°C; IR (KBr): 1770, 1740 (CO); ^{1}H NMR ($CDCl_3$): 4.65 (1H, dd, J=10.9, 1.6 Hz, 3a-H), 5.07 (1H, d, J=10.9 Hz, 6a-H), 6.92 (1H, d, J=1.6 Hz, 3-H), 6.98–7.52 (10H, ov, Ph-H); ^{13}C NMR ($CDCl_3$): 55.4, 63.3, 114.3, 121.7, 126.3, 129.1, 129.2, 129.3, 131.1, 133.5, 144.4, 171.1, 172.1. Anal. calcd for $C_{17}H_{13}N_3O_2$ (291.3): C, 70.09; H, 4.50; N, 14.42. Found: C, 70.08; H, 4.41; N, 14.38.

4.4.5. NH-Azomethine imine cycloadduct 7b. Colorless crystals without recrystallization; mp 177°C; IR (KBr): 3240 (NH), 1775, 1710, 1700, 1630 (CO), ^{1}H NMR ($CDCl_3$): 3.07 (3H, s, NCH_3), 3.61 (1H, dd, J=9.2, 8.2 Hz, 3a′-H), 4.60 (1H, dd, J=12.5, 9.2 Hz, 3-H), 4.64, 4.85 (each 1H, each d, J=15.8 Hz, NCH_2Ph), 4.96 (1H, d, J=9.2 Hz, 6a′-H), 6.35 (1H, d, J=12.5 Hz, exchangeable with D_2O, 2′-NH), 6.88–6.97 (2H, ov, Ph-H and 7-H), 7.19–7.29 (9H, ov, Ph-H), 7.31–7.42 (2H, ov, Ph-H and 9-H), 7.45–7.55 (4H, ov, Ph-H), 7.62 (1H, br t, J=6.9 Hz, 8-H), 8.77 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 39.5, 50.8, 56.8, 61.4, 70.8, 89.7, 113.6, 114.7, 120.7, 124.7, 126.9, 127.3, 127.4, 128.5, 128.6, 128.9, 129.0, 129.1, 132.4, 136.6, 137.4, 148.5, 150.9, 159.1, 165.0, 173.9, 175.1. Anal. calcd for $C_{33}H_{28}N_6O_3$ (556.6): C, 71.21; H, 5.07; N, 15.10. Found: C, 71.09; H, 5.07; N, 15.15.

4.4.6. Dehydrogenated product 8b. Orange crystals from EtOH; mp 280–281°C; IR (KBr): 1770, 1700, 1650 (CO); ^{1}H NMR ($CDCl_3$): 2.76 (3H, s, NCH_3), 4.75, 5.27 (each 1H, each d, J=15.2 Hz, NCH_2Ph), 5.20 (1H, d, J=11.2 Hz, 3a′-H), 6.09 (1H, d, J=11.2 Hz, 6a′-H), 6.86–7.00 (2H, ov, 7-H and Ph-H), 7.18 (2H, m, Ph-H), 7.30–7.62 (10H, ov, 8-H, 9-H and Ph-H) and 8.86 (1H, br d, J=7.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$) 39.6, 54.8, 55.7, 64.6, 86.8. 112.7, 114.4, 121.0, 124.4, 126.1, 127.2, 127.4, 127.6, 128.5, 128.8, 129.1, 129.1, 131.3, 136.7, 137.7, 141.9, 145.1, 148.6, 158.8, 160.6, 171.5, 172.7. Anal. calcd for $C_{33}H_{26}N_6O_3$ (554.6): C, 71.47; H, 4.73; N, 15.15. Found: C, 71.56; H, 4.80; N, 15.11.

4.4.7. 2-(*N*-Methylbenzylamino)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (9b). Colorless crystals from hexane/EtOAc; mp 118–119°C; IR (KBr): 1650 (CO); ^{1}H NMR ($CDCl_3$): 3.06 (3H, s, NCH_3), 4.90 (2H, br s, NCH_2Ph), 5.60 (1H, s, 3-H), 6.86 (1H, m, 8-H), 7.22–7.36 (6H, ov, Ph-H and 9-H), 7.57 (1H, m, 7-H), 8.90 (1H, br d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$) 35.7, 52.6, 80.6, 112.2, 124.3, 127.2, 127.2, 127.4, 128.6, 136.2, 137.7, 150.5, 158.5, 161.2. Anal. calcd for

$C_{16}H_{15}N_3O$ (265.3): C, 72.43, H, 5.70; N, 15.84. Found: C, 72.35; H, 5.66; N, 15.70.

4.4.8. NH-Azomethine imine cycloadduct 7d. Colorless needles from hexane/EtOAc; mp 226°C; IR (KBr): 3260 (NH), 1775, 1720, 1710, 1630 (CO); ^{1}H NMR ($CDCl_3$): 1.38 (3H, t, J=7.3 Hz, OCH_2CH_3), 3.73 (1H, dd, J=8.9, 7.9 Hz, 3a′-H), 4.53 (2H, m, OCH_2CH_3), 4.91 (1H, dd, J=12.9, 8.9 Hz, 3′-H), 5.00 (1H, d, J=7.9 Hz, 6a′-H), 6.59 (1H, d, J=12.5 Hz, exchangeable with D_2O, 2′-NH), 6.94 (1H, t, J=6.9 Hz, Ph-H), 7.06 (1H, m, 7-H), 7.25–7.48 (10H, ov, Ph-H and 5-H), 7.71 (1H, m, 8-H), 8.92 (1H, br d, J=6.9 Hz, 6-H); ^{13}C NMR ($CDCl_3$) 14.7, 51.4, 57.9, 63.2, 69.9, 90.0, 114.6, 115.0, 120.5, 124.8, 126.7, 127.3, 128.5, 128.9, 129.1, 132.1, 137.3, 149.7, 150.9, 158.5, 165.5, 173.8, 174.8. Anal. calcd for $C_{27}H_{23}N_5O_4$ (481.5): C, 67.35; H, 4.81; N, 14.54; found C, 67.46; H, 4.86; N, 14.47.

4.4.9. Dehydrogenated product 8d. Yellow needles from propan-2-ol; mp 134–136°C; IR (KBr): 1770, 1720, 1710, 1640 (CO); ^{1}H NMR ($CDCl_3$) 1.42 (3H, t, J=7.2 Hz, CH_2CH_3), 4.49–4.66 (2H, m, CH_2CH_3), 5.25 (1H, d, J=11.2 Hz, 3a′-H), 5.72 (1H, J=11.2 Hz, 6a′-H), 6.97 (1H, br t, J=7.4 Hz, Ph-H), 7.15 (1H, td, J=6.9, 1.3 Hz, 7-H), 7.26–7.74 (10H, ov, Ph-H and 9-H), 7.79 (1H, m, 8-H), 9.12 (1H, dd, J=6.6, 1.0 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 16.1, 56.1, 64.9, 65.4, 91.1, 115.8, 116.5, 122.5, 126.3, 126.9, 127.7, 129.7, 130.1, 130.4, 130.7, 132.8, 139.5, 146.1, 151.1, 158.7, 166.8, 172.7, 173.8. Anal. calcd for $C_{27}H_{21}N_5O_4$ (479.5): C, 67.63; H, 4.41; N, 14.61. Found: C, 67.55; H, 4.51; N, 14.44.

4.4.10. NH-Azomethine cycloadduct *endo*-7e and *exo*-7e′. Although these two compounds were not attained to isolate to each other as pure forms, the structures were assigned to be *endo*- and *exo*-cycloadduct, respectively, on the basis of their ^{1}H NMR spectroscopic data as well as a chemical conversion. Elementary analysis of the 5:1 mixture of *endo*-**7e** and *exo*-**7e′** provided good results. Anal. calcd for $C_{26}H_{21}N_5O_3$ (451.5): C, 69.17; H, 4.69; N, 15.51. Found: C, 69.22; H, 4.82; N, 15.66.

^{1}H NMR ($CDCl_3$): assigned signals for major isomer *endo*-**7e**: 2.59 (3H, s, 2-CH_3), 3.75 (1H, dd, $J_{3a'-3'}$=8.9 Hz [*cis*], $J_{3a'-6a'}$=7.9 Hz [*cis*], 3a′-H), 4.68 (1H, dd, $J_{3'-2'}$=12.5 Hz, $J_{3'-3a'}$=8.9 Hz, 3′-H), 5.06 (1H, d, $J_{6a'-3a'}$=7.9 Hz, 6a′-H), 6.63 (1H, d, $J_{2'-3'}$=12.5 Hz, exchangeable with D_2O, 2′-NH), 6.98 (1H, m, Ph-H), 7.16 (1H, m, 7-H), 7.28–7.79 (11H, ov, 8-H, 9-H, Ph-H), 8.92 (1H, m, 6-H); assigned signals for minor isomer *exo*-**7e′**: 2.70 (3H, s, 2-CH_3), 4.49 (1H, dd, $J_{3a'-3'}$=7.3 Hz [*trans*], $J_{3a'-6a'}$=7.9 Hz [*cis*], 3a′-H), 4.84 (1H, d, $J_{6a'-3a'}$=7.9 Hz, 6a′-H), 4.94 (1H, dd, $J_{3'-2'}$=12.2 Hz, J_{3-3a}=7.3 Hz, 3′-H), 5.66 (1H, d, $J_{2'-3'}$=12.2 Hz, exchangeable with D_2O, 2′-NH).

The treatment of the 5:1 mixture of *endo*-**7e** and *exo*-**7e′** (0.15 g, 0.33 mmol) with 10% palladium/carbon (0.050 g) in refluxing 1,4-dioxane (5 mL) for 8 h gave dehydrogenated product **8e** (0.14 g, 94%).

4.4.11. Dehydrogenated product 8e. Yellow prisms from EtOH/hexane; mp 142–144°C (with decomposition); IR (KBr): 1770, 1710, 1660 (CO); ^{1}H NMR ($CDCl_3$): 2.72 (3H, s, 2-CH_3), 5.29 (1H, d, J=11.1 Hz, 3a′-H), 6.00 (1H, d, J=11.1 Hz, 6a′-H), 7.01 (1H, td, J=7.4, 1.3 Hz, 7-H), 7.19 (1H, td, J=6.9, 1.0 Hz, Ph-H), 7.26–7.35 (3H, ov, Ph-H and 9-H), 7.49–7.56 (3H, ov, Ph-H and 8-H), 7.80 (1H, m, 8-H), 8.83 (1H, d, J=6.6 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 24.9, 54.6, 64.6, 106.2, 114.4, 115.9, 121.6, 126.1, 126.2, 127.3, 128.8, 131.3, 136.9, 140.8, 144.5, 149.4, 164.9, 171.2, 172.3. Anal. calcd for $C_{26}H_{19}N_5O_3$ (449.5): C, 69.48; H, 4.26; N, 15.58. Found: C, 69.32; H, 4.52; N, 15.59.

4.4.12. NH-Azomethine imine cycloadduct 12. Colorless crystals without recrystallization; mp 199–200°C; IR (KBr): 3240 (NH), 1770, 1720, 1710, 1660 (CO); ^{1}H NMR ($CDCl_3$): 1.91 (4H, ov, $N(CH_2CH_2)_2$), 3.06 (3H, s, NCH_3), 3.50 (1H, dd, J=9.2, 7.6 Hz, 3a′-H), 3.67 (4H, ov, $N(CH_2CH_2)_2$), 4.60 (1H, dd, J=12.2, 9.2 Hz, 3′-H), 4.89 (1H, d, J=7.6 Hz, 6a′-H), 6.25 (1H, d, J=12.2 Hz, exchangeable with D_2O, 2′-NH), 6.83 (1H, m, 7-H), 6.90 (1H, m, Ph-H), 7.27 (5H, ov, 9-H and Ph-H), 7.55 (1H, m, 8-H), 8.68 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 25.3, 25.7, 50.4, 51.4, 60.9, 70.4, 86.6, 112.6, 114.5, 120.4, 124.4, 126.8, 129.1, 136.2, 148.4, 150.8, 158.6, 161.1, 175.1, 176.1. Anal. calcd for $C_{24}H_{24}N_6O_3$ (444.5): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.58; H, 5.54; N, 18.80.

4.4.13. Dehydrogenated product 13. Yellow prisms from EtOH; mp 260–263°C (with decomposition); IR (KBr): 1770, 1720, 1660 (CO); ^{1}H NMR ($CDCl_3$): 1.75–1.82, 1.82–2.02 (each 2H, each br, $N(CH_2CH_2)_2$), 2.8–3.2, 3.53–3.59 (each 2H, each br, $N(CH_2CH_2)_2$), 6.83 (1H, td, J=7.0, 1.3 Hz, Ph-H), 6.96 (1H, t, J=7.3 Hz, 7-H), 7.26–7.59 (6H, ov, Ph-H and 9-H), 8.83 (1H, dd, J=7.3, 0.7 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 25.3, 25.4, 49.9, 55.7, 64.9, 86.1, 112.2, 114.4, 121.1, 123.8, 124.4, 127.3, 129.1, 136.4, 141.9, 145.3, 148.9, 157.5, 172.9, 174.1. Anal. calcd for $C_{24}H_{22}N_6O_3$ (442.5): C, 65.14; H, 5.01; N, 19.00. Found: C, 65.22; H, 5.21; N, 18.91.

4.4.14. NH-Azomethine imine cycloadduct 15. Yellow needles from hexane/EtOAc; mp 187–188°C; IR (KBr): 3210 (NH), 1730, 1720, 1650 (C=O); ^{1}H NMR ($CDCl_3$): 1.79–1.84 (4H, ov, $N(CH_2CH_2)_2$), 1.94–1.99 (4H, ov, $N(CH_2CH_2)_2$), 3.57, 3.89 (each 3H, each s, OCH_3), 4.46 (1H, dd, J=12.5, 8.9 Hz, 3′-H), 4.71 (1H, dd, J=8.9, 6.3 Hz, 4′-H), 4.82 (1H, d, J=6.3 Hz, 5′-H), 5.66 (1H, d, J=12.5 Hz, exchangeable with D_2O, 2′-NH), 6.81–6.86 (2H, m, Ph-H and 7-H), 7.15 (2H, m, Ph-H), 7.22–7.28 (3H, ov, Ph-H and 9-H), 7.55 (1H, m, 8-H), 8.86 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 25.6, 50.4, 52.2, 52.8, 53.0, 61.4, 70.4, 87.2, 112.2, 113.5, 119.3, 124.3, 127.0, 128.9, 136.1, 148.5, 150.6, 158.1, 160.6, 172.6, 172.8. Anal. calcd for $C_{25}H_{27}N_5O_5$ (477.5): C, 62.88; H, 5.70; N, 14.67. Found: C, 62.83; H, 5.76; N, 14.56.

4.4.15. Dehydrogenated product 16. Although this compound was not attained to isolate as a pure form, the structure was assigned on the basis of its ^{1}H NMR spectra: ^{1}H NMR ($CDCl_3$): 1.61, 1.83 (each 2H, each m, $N(CH_2CH_2)_2$), 3.38, 3.62 (each 2H, each m, $N(CH_2CH_2)_2$), 3.71, 3.78 (each 3H, each s, OCH_3), 5.17 (1H, d, J=6.6 Hz, 4′-H), 5.47 (1H, d, J=6.6 Hz, 5′-H), 6.77–6.97 (2H, ov, Ph-H and 7-H), 7.03 (2H, br d,

J=7.6 Hz, Ph-H), 7.247.30 (3H, ov, Ph-H and 9-H), 7.53 (1H, m, 8-H), 8.79 (1H, dd, J=6.3, 0.7 Hz, 6-H).

In order to obtain product **16**, adduct **15** (0.10 g, 0.21 mmol) was treated with 10% palladium/carbon (0.040 g) in refluxing 1,4-dioxane (5 mL) for 2 h. Usual work-up did not give the desired **16** but a further dehydrogenated product pyrazole **17** (0.077g, 78%).

4.4.16. Pyrazole 17. Colorless prisms from propan-2-ol; mp 194–195°C; IR (KBr): 1720, 1715, 1670 (CO); ^{1}H NMR ($CDCl_3$): 1.81 (4H, br, $N(CH_2CH_2)_2$), 3.35 (4H, br, $N(CH_2CH_2)_2$), 3.79, 3.86 (each 3H, each s, OCH_3), 6.81 (1H, t, J=6.9 Hz, 7-H), 7.27 (1H, m, Ph-H), 7.14–7.57 (6H, ov, Ph-H and 7- and 9-H), 8.86 (1H, J=7.3 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 25.4, 49.1, 51.9, 53.1, 86.5, 111.9, 117.3, 124.2, 124.3, 127.8, 128.7, 129.1, 136.1, 136.4, 139.1, 149.2, 149.4, 157.5, 157.9, 161.3, 162.7. Anal. calcd for $C_{25}H_{23}N_5O_5$ (473.5): C, 63.41; H, 4.90; N, 14.79. Found: C, 63.50; H, 4.79; N, 14.70.

4.4.17. NH-Azomethine imine cycloadduct 19. Pale yellow crystals from hexane/EtOAc; mp 185–187°C; IR (KBr): 3230 (NH), 1730, 1720, 1650 (CO); ^{1}H NMR ($CDCl_3$): 1.90 (4H, br, $N(CH_2CH_2)_2$), 3.60 (4H, br, $N(CH_2CH_2)_2$), 3.66, 3.84 (each 3H, each s, OCH_3), 3.99 (1H, dd, J=7.3, 5.9 Hz, 4′-H), 4.27 (1H, dd, J=12.9, 5.9 Hz, 3′-H), 4.42 (1H, d, J=7.3 Hz, 5′-H), 6.81–6.88 (3H, ov, Ph-H, 2′-NH and 7-H), 7.09 (2H, m, Ph-H), 7.24 (3H, ov, Ph-H and 9-H), 7.55 (1H, m, 8-H), 8.90 (1H, m, 6-H); ^{13}C NMR ($CDCl_3$): 25.6, 50.6, 52.5, 55.8, 61.5, 70.2, 87.9, 112.5, 114.3, 119.6, 124.3, 127.1, 128.7, 136.2, 148.4, 152.1, 158.3, 161.6, 170.1, 171.6. Anal. calcd for $C_{25}H_{27}N_5O_5$ (477.5): C, 62.88; H, 5.70; N, 14.67. Found: C, 62.85; H, 5.78; N, 14.61.

4.5. General procedures for the reaction of hydrazone 3 with dipolarophiles in the presence of PPTS

A solution of hydrazone **3a** (0.20 g, 0.60 mmol), maleimide **6** (0.10 g, 0.60 mmol) and PPTS (0.15 g, 0.60 mmol) in benzene (3 mL) was heated at reflux for 20 h. Usual work-up with silica-gel chromatography with hexane/EtOAc (6/1) as an eluent afforded 2-pyrazoline **10** (0.16 g, 90%) and pyridopyrimidine **9a** (0.13 g, 90%), respectively.

4.6. Conversion of 9a into the starting aldehyde 2a

To a dry dimethyl formamide (2.7 mL, 35.1 mmol) cooled below 10°C was added phosphorous oxychloride (2.02 g, 13.7 mmol) for 10 min. To the resultant solution was added pyrrolidinylpyridopyrimidine **9a** (0.86 g, 4.0 mmol) and the mixture was heated at 90°C for 1 h. After cooling, the solution was poured into ice-water (40 mL) and basified to 8.5 with 2N NaOH aq. The solution was extracted with toluene (50 mL×2), the organic layer was washed with brine (50 mL×3), dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give aldehyde **2a** (0.86 g, 77%).

4.6.1. 2-Pyrazoline 25. Colorless needles from hexane/EtOAc; mp 168–169°C; IR (KBr): 1770, 1720, 1650 (CO); ^{1}H NMR ($CDCl_3$): 3.04 (3H, s, 5-CH_3), 4.50 (1H, dd, J=10.9 Hz, 6a-H), 6.84 (1H, d, J=2.0 Hz, 3-H), 6.99 (1H, m, Ph-H), 7.34 (2H, m, Ph-H), 7.44 (2H, m, Ph-H); ^{13}C NMR ($CDCl_3$): 25.4, 55.4, 63.2, 114.2, 114.6, 121.5, 129.2, 133.3, 144.4, 172.1, 173.1. Anal. calcd for $C_{12}H_{11}N_3O_2$ (229.2): C, 62.87; H, 4.84; N, 18.33. Found: C, 62.85; H, 4.88; N, 18.17.

4.6.2. Dimethyl 1-phenyl-2-pyrazoline-4,5-dicarboxylate (26). Yellow oil; IR (NaCl): 1725 (CO); ^{1}H NMR ($CDCl_3$): 3.78, 3.81 (each 3H, each s, OCH_3×2), 4.32 (1H, dd, J=7.3, 2.0 Hz, 4-H), 5.05 (1H, d, J=2.0 Hz, 3-H), 6.92 (1H, t, J=7.3 Hz, Ph-H), 7.09 (2H, m, Ph-H), 7.28 (2H, m, Ph-H); ^{13}C NMR ($CDCl_3$): 53.2, 57.3, 62.7, 113.5, 120.6, 123.8, 129.1, 134.1, 144.3, 168.0, 170.7; HRMS (EI): m/z=262.0938. Calcd for $C_{13}H_{14}N_2O_4$: 262.0953. Anal. calcd for $C_{13}H_{14}N_2O_4$ (262.3): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.87; H, 5.10; N, 10.72.

4.6.3. Dimethyl 1-phenylpyrazole-4,5-dicarboxylate (27). Colorless needles from hexane/EtOAc; mp 73–75°C; IR (KBr): 1720 (CO); ^{1}H NMR ($CDCl_3$): 3.87, 3.88 (each 3H, each s, OCH_3×2), 7.45–7.51 (5H, ov, Ph-H), 8.05 (1H, s, 3-H); ^{13}C NMR ($CDCl_3$): 51.9, 53.4, 115.6, 123.8, 129.0, 129.1, 129.3, 136.7, 141.3, 161.3, 162.2. Anal. calcd for $C_{13}H_{12}N_2O_4$ (260.2): C, 60.00; H, 4.61; N, 10.76. Found C, 59.90; H, 4.61; N, 10.74.

4.6.4. Ethyl 1-phenyl-2-pyrazoline-4-carboxylate (28). Pale yellow oil; IR (NaCl): 1720 (CO); ^{1}H NMR ($CDCl_3$): 1.30 (3H, t, J=7.1 Hz, CH_2CH_3), 3.88 (1H, dd, J_{gem}=11.5 Hz, J_{4-5}=8.9 Hz, 5-H), 3.95–4.15 (2H, ov, 4- and 5-H), 4.23 (2H, q, J=7.1 Hz, CH_2CH_3), 6.79 (1H, d, J_{3-4}=1.7 Hz), 6.87 (1H, t, J=7.3 Hz, Ph-H), 7.05 (2H, d, J=7.3 Hz, Ph-H), 7.24–7.31 (2H, m, Ph-H); ^{13}C NMR ($CDCl_3$): 14.1, 49.0, 51.6, 61.8, 113.0, 119.7, 129.1, 136.0, 145.2, 169.1; HRMS (EI): m/z=218.1061. Calcd for $C_{12}H_{14}N_2O_2$: 218.1055.

4.6.5. Ethyl 1-phenylpyrazole-4-carboxylate (29). Colorless needles from hexane/EtOAc; mp 96–99°C; IR (KBr): 1720 (CO); ^{1}H NMR ($CDCl_3$): 1.38 (3H, t, J=7.3 Hz, OCH_2CH_3), 4.34 (2H, q, J=7.3 Hz, OCH_2CH_3), 7.36 (1H, m, Ph-H), 7.48 (2H, m, Ph-H), 7.71 (2H, m, Ph-H), 8.10 (1H, s, 3-H), 8.41 (1H, s, 5-H); ^{13}C NMR ($CDCl_3$): 14.4, 60.4, 116.9, 119.6, 127.5, 129.6, 130.0, 139.4, 142.1, 162.8. Anal. calcd for $C_{12}H_{12}N_2O_4$ (216.1): C, 66.65; H, 5.59; N, 12.96. Found C, 66.44; H, 5.67; N, 12.91.

4.6.6. Ethyl 1-phenyl-2-pyrazoline-5-carboxylate (30). Yellow oil; IR (NaCl): 1720 (CO); ^{1}H NMR ($CDCl_3$): 1.22 (3H, t, J=7.3 Hz, OCH_2CH_3), 3.11 (1H, ddd, J=17.8, 7.3, 1.7 Hz, 4-H), 3.35 (1H, ddd, J=17.8, 12.5, 1.7 Hz, 4-H), 4.21 (2H, q, J=7.3 Hz, OCH_2CH_3), 4.59 (1H, dd, J=12.5, 7.3 Hz, 5-H), 6.71 (1H, t, J=1.7 Hz, 3-H), 6.87 (1H, m, Ph-H), 7.03 (2H, m, Ph-H), 7.26 (2H, m, Ph-H); ^{13}C NMR ($CDCl_3$): 14.1, 39.7, 60.2, 61.7, 113.1, 119.9, 129.1, 138.5, 145.0, 171.6; HRMS (EI): m/z=218.1065. Calcd for $C_{12}H_{14}N_2O_2$: 218.1055.

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