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Reaction of 2-substituted-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oximes with electron-deficient olefins and acetylenes

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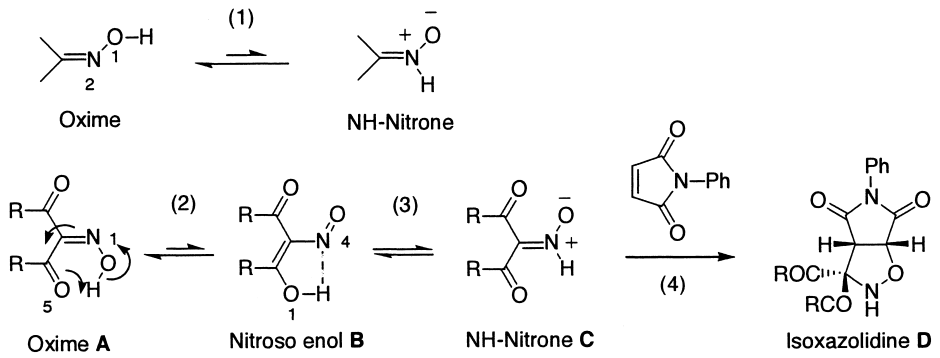
Abstract—A facile oxime–nitrone isomerization through the 1,2-hydrogen shift in 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oximes is discussed. The resultant NH-nitrones are trapped by maleimides to afford intermolecular cycloadducts. The reaction of the oximes with electron-deficient acetylenes undergoes via another path initiated by a nucleophilic attack of the oxime to acetylene moiety. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Since the concept of the thermal isomerization of oxime to nitrone through the 1,2-hydrogen shift was proposed by Grigg and co-workers in 1984[1] and the existence of the resultant NH-nitrone was elucidated by forming intramolecular cycloaddition products, extensive investigations on the synthesis of highly functionalized isoxazolidine derivatives have been developed by many groups.[2] Nevertheless, the application of the resultant NH-nitrones to an intermolecular cycloaddition reaction with dipolarophiles has not been accomplished except for one report;[1c] only the 2-oxime **A** of 1,2,3-tricarbonyl system underwent 1,5-proton transfer in refluxing toluene followed by 1,4-proton transfer leading to the corresponding NH-nitrone **C**, which was trapped by *N*-phenyl maleimide (NPMI) as an intermolecular (1:1) cycloadduct **D** (Scheme 1). However, other oximes including some α-keto oximes failed to give any cycloadducts with NPMI even under more harsh conditions.

As a part of our projects to generate the NH-1,3-dipoles through the hydrogen shift and to perform the cycloaddition reaction of the dipoles,[3] we reported recently a facile hydrazone–azomethine imine isomerization at the periphery of a heterocyclic system and an intermolecular cycloaddition reaction of the azomethine imine with olefinic dipolarophiles.[4] Therein, the formation of an internal hydrogen bond between the NH in the dipole moiety and the carbonyl oxygen in the heterocyclic system would be essential for the facile isomerization process (Scheme 2).



Scheme 1. *Reactions*. (1) 1,2-H shift; (2) 1,5-H shift; (3) proton transfer; (4) intermolecular cycloaddition reaction.

Keywords: oxime–nitrone isomerization; 1,3-dipolar cycloaddition; Michael addition.
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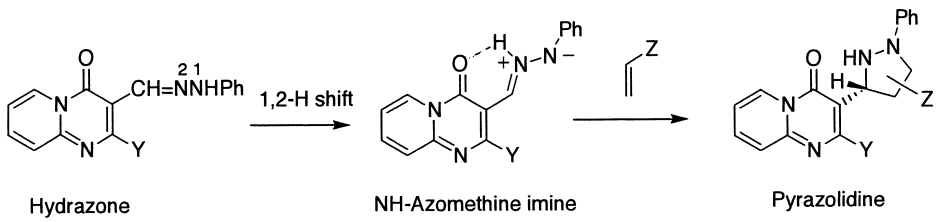
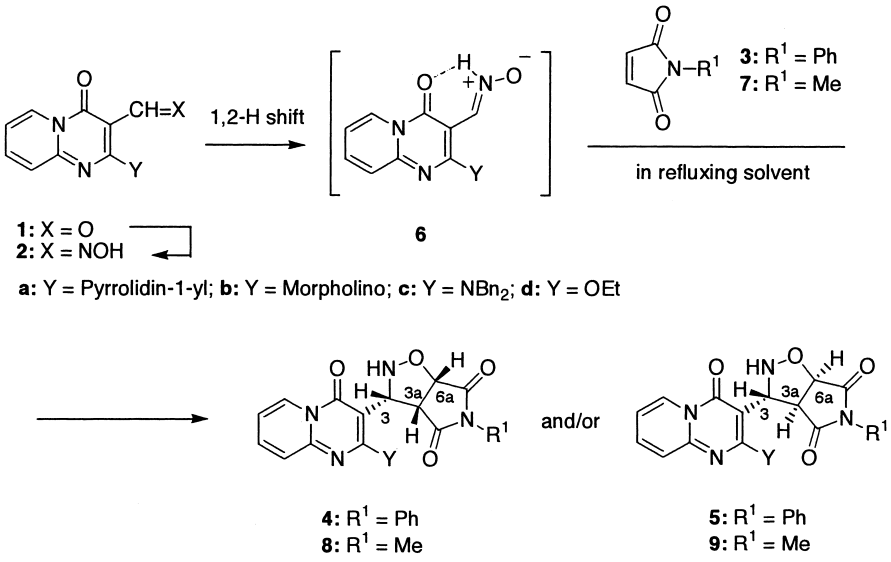


Scheme 2.

In this paper, we want to report the facile oxime–nitrone isomerization in the above system and the intermolecular cycloaddition of the nitrone with NPMI. In the reaction of the oxime with acetylenic dipolarophiles another reaction pathway will be proposed.

2. Results and discussion

In order to elucidate the scope and features of the oxime–nitrone isomerization in 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde system, four oximes **2a–d** were prepared and examined the thermal behavior in the presence of dipolarophiles (Scheme 3). The reaction of oxime **2a** with NPMI (**3**) in refluxing benzene for 36 h gave isoxazolidine derivative **4a** in 82% yield as a single product. A similar reaction in refluxing ethanol or acetonitrile also gave **4a** in 66 and 68% yields, respectively. The structure of **4a** was deduced on the basis of analytical and spectroscopic data. Its stereochemistries were fully characterized by COSY spectra as well as the coupling constants; for example, the relative configurations among the three methine protons (3-H, 3a-H, and 6a-H) in **4a** were deduced to be all *cis* on the basis of the coupling constants (J_{3-3a}=8.9 Hz, J_{3a-6a}=7.9 Hz). The formation of **4a** is easily explained by an *endo*-approaching cycloadduct to the hydrogen-bonded NH-nitrone **6**. While a similar reaction of oximes **2b** and **2c** with **3** in benzene gave two diastereomeric isoxazolidine derivatives (**4b** and **5b**) and (**4c** and **5c**), respectively, the reaction of oxime **2d** with **3** gave **4d** as a single product. The relative configurations among the three methine protons of **5b** and **5c** were deduced to be *trans–cis* from the coupling constants (J_{3-3a}=6–7 Hz, J_{3a-6a}=7–8 Hz), and the formation of **5** was responsible for an *exo*-approach of **3** to the NH-nitrone **6**. These stereochemical assignments were confirmed by nuclear Overhauser effect (NOE) measurements of similar systems as described later. A similar reaction of oxime **2a** with *N*-methyl maleimide (**7**) under same conditions gave two diastereomeric isoxazolidine derivatives **8** and **9** in 68 and 4% yields, respectively (Table 1). The stereochemistries



Scheme 3.

Table 1. Reaction of oximes **2** with maleimides **3** and **7**

Run	Oxime	Y	Maleimide	Solvent	Time (h)	Products (yield, %)
1	**2a**	Pyrrolidin-1-yl	**3**	Benzene	36	**4a** (82)
2	**2a**	Pyrrolidin-1-yl	**3**	Ethanol	36	**4a** (66)
3	**2a**	Pyrrolidin-1-yl	**3**	Acetonitrile	24	**4a** (68)
4	**2b**	Morpholino	**3**	Benzene	24	**4b** (66), **5b** (3)
5	**2c**	NBn_2	**3**	Benzene	24	**4c** (53), **5c** (26)
6	**2d**	OEt	**3**	Benzene	24	**4d** (87)
7	**2a**	Pyrrolidin-1-yl	**7**	Benzene	36	**8** (68), **9** (4)

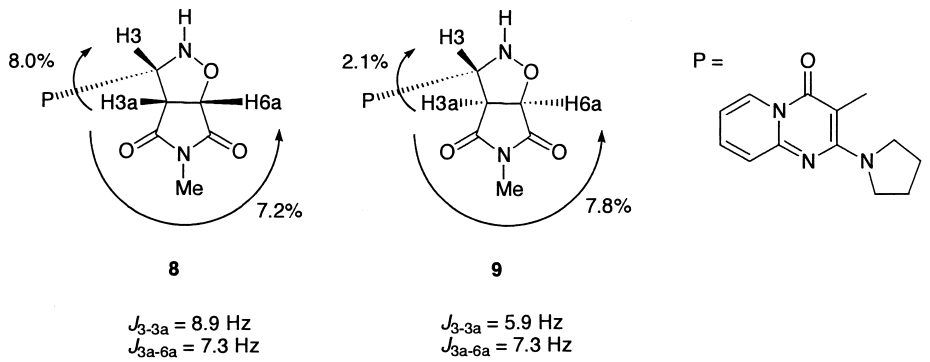


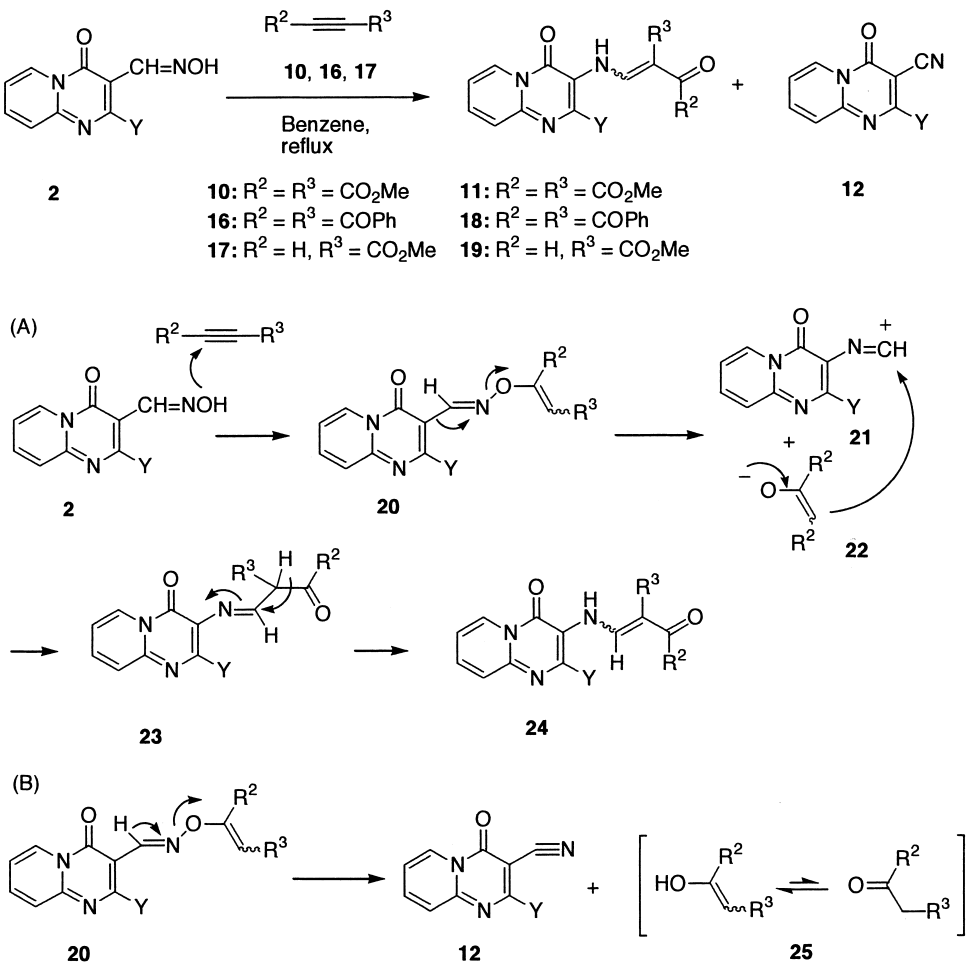
Figure 1. Selected NOE signal enhancements and coupling constants among the isoxazolidine-ring protons of cycloadducts **8** and **9**.

of **8** (*endo*-adduct) and **9** (*exo*-adduct) were also confirmed by the coupling constants as well as NOE measurements (Fig. 1).

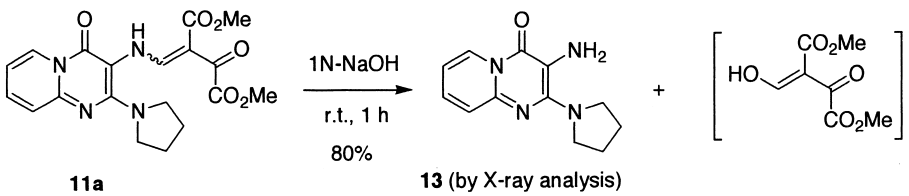
To obtain further information on the reaction features, the reaction of oxime **2a** with other olefinic dipolarophiles such as dimethyl fumarate, dimethyl maleate, and ethyl acrylate under several conditions were examined; in the reactions of **2a** in benzene under reflux the unreacted **2a** was recovered in more than 90% yields. Similar reactions at elevated temperature (e.g. in toluene under reflux) gave mixtures of many products probably due to decomposition of **2a**.

As mentioned above, we have reported that the facile oxime–nitrone isomerization in 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde system **2** and the resulting NH-nitrones **6** are allowed to react with maleimides **3** and **7** to give intermolecular cycloadducts. This is the second example on the intermolecular cycloaddition of NH-nitrones, but, unfortunately, other olefinic dipolarophiles than maleimides **3** and **7** could not trap the NH-nitrone intermediates similarly to the first example (Scheme 4).[1c]

Our next concern was focused on the reaction of NH-nitrones **6** with acetylenic dipolarophiles; the reaction of oxime **2a** with dimethyl acetylenedicarboxylate (DMAD:



Scheme 4.



Scheme 5.

10) in benzene under reflux for 2 h gave a (1:1) adduct **11a** (84%) and a trace of 4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (**12a**). A similar reaction in ethanol or acetonitrile under reflux gave almost same results. To obtain more information on the structure of **11a**, some chemical conversions of **11a** were examined; the alkaline hydrolysis of **11a** gave 3-amino-2-(pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**13**) in 80% yield. The structure of **13** was also suggested on the basis of analytical and spectroscopic data and confirmed finally by an X-ray single crystal analysis. From these findings as well as the results of the reaction of benzaldoxime and DMAD,[5] the structure of **11a** was deduced to be 3-oxo-3-[{4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}amino]-methylenesuccinic acid dimethyl ester. The structure of **11a** was confirmed by an alternate synthesis from **13** and 2-ethoxymethylene-3-oxosuccinic acid dimethyl ester (**15**) (Scheme 5).

The reaction of oxime **2a** with dibenzoyl acetylene (**16**) and methyl propiolate (**17**) in refluxing benzene gave **18** and **19**, respectively. A similar reaction of oxime **2b**–**d** with DMAD (**10**) also gave **11b**–**d** and **12b**–**d**, respectively. These results are summarized in Table 2.

Table 2. Reaction of oximes **2** with electron-deficient acetylenes **10**, **16**, and **17**

Run[a]	Oxime	Y	Acetylene	Time (h)	Products (yield, %)
1	**2a**	Pyrrolidin-1-yl	**10**	2	**11a** (84), **12a** (trace)
2	**2b**	Morpholino	**10**	1.5	**11b** (79), **12b** (trace)
3	**2c**	NBn_2	**10**	2	**11c** (97), **12c** (trace)
4	**2d**	OEt	**10**	21	**11d** (20), **12d** (52)
5	**2a**	Pyrrolidin-1-yl	**16**	1.5	**18** (98), **12a** (trace)
6	**2a**	Pyrrolidin-1-yl	**17**	4	**19** (12), **12a** (39)

[a] Reaction conditions: benzene, reflux.

The formation of **11**, **18**, and **19** was explained by assuming a nucleophilic attack of oxime to acetylene moiety as shown in Scheme 6. In the Michael type adduct **20**, a Beckmann type cleavage through path (a) gave carbocation **21** and enolate **22**. The enolate **22** performed a nucleophilic attack to **21** to give imine **23**, which was isomerized to enamine **24**. On the other hand, the elimination of ketone **25** from **20** [path (b)] gave nitrile derivative **12**.

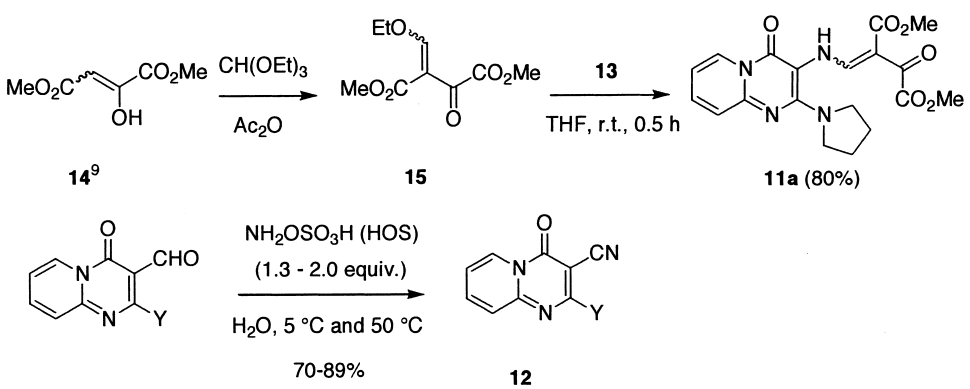
3. Conclusion

We have reported the facile oxime–nitrone isomerization and the second example on the intermolecular cycloaddition of the resultant NH-nitrones with maleimides. In the reaction of the oximes with acetylenic dipolarophiles, a nucleophilic addition of oxime to acetylene moiety was preferable to the expecting 1,2-hydrogen shift leading to NH-nitrones. 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.



Scheme 6.

Splitting patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet, m, multiplet; 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. General procedures for the preparation of oximes 2

A solution of 4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde (**1a**: 0.71 g, 2.9 mmol), hydroxylamine hydrochloride (0.26 g, 1.3 equiv.), and triethylamine (0.62 mL, 1.5 equiv.) in methanol (MeOH) (10 mL) was stirred at room temperature for 8 h. The solvent was evaporated to dryness, which was extracted with dichloromethane (20 mL). The organic layer was dried and the solvent was evaporated to give oxime **2a** (0.62 g, 83%).

4.2.1. 4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oxime (2a). Yellow plate from MeOH; mp 209–210°C; IR (KBr): 3250 (OH), 1660, 1620 (CO); ^{1}H NMR ($CDCl_3$): 1.93 [4H, br, $N(CH_2CH_2)_2$], 3.60 [4H, br, $N(CH_2CH_2)_2$], 6.28 (1H, ddd, *J*=1.2, 6.7, 7.6 Hz, 7-H), 7.27 (1H, ddd, *J*=0.7, 1.2, 8.6 Hz, 9-H), 7.56 (1H, ddd, *J*=1.7, 6.7, 8.6 Hz, 8-H), 8.17 (1H, s, –CH=N–), 8.1–8.9 (1H, br, OH), 8.87 (1H, ddd, *J*=0.7, 1.7, 7.6 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 25.55, 50.84, 88.01, 112.27, 124.33, 127.80, 136.48, 146.42, 148.81, 157.75, 157.97. Anal. calcd for $C_{13}H_{14}N_4O_2$ (258.3): C, 60.45; H, 5.46; N, 21.69. Found: C, 60.48; H, 5.39; N, 21.62.

4.2.2. 2-Morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oxime (2b). 85%; Pale yellow prisms from propan-2-ol (2-PrOH); mp 205°C; IR (KBr): 3260 (OH), 1660, 1620 (CO); ^{1}H NMR ($CDCl_3$): 3.62 [4H, br t, *J*=5.0 Hz, $N(CH_2CH_2)_2O$], 3.81 [4H, br t, *J*=5.0 Hz, $N(CH_2CH_2)_2O$], 6.99 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.38 (1H, ddd, *J*=0.7, 1.3, 8.6 Hz, 9-H), 7.67 (1H, ddd, *J*=1.7, 6.9, 8.6 Hz, 8-H), 8.24 (1H, s, –CH=N–), 9.04 (1H, ddd, *J*=0.7, 1.7, 6.9 Hz, 6-H), 9.4–10.5 (1H, br, OH); ^{13}C NMR ($CDCl_3$): 49.90, 66.88, 91.57, 113.87, 124.82, 128.18, 137.07, 144.89, 149.06, 156.84, 162.16. Anal. calcd for $C_{13}H_{14}N_4O_3$ (274.3): C, 56.93; H, 5.14; N, 20.43. Found: C, 56.91; H, 5.20; N, 20.14.

4.2.3. 2-(*N*,*N*-Dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oxime (2c). 55%; Pale yellow prisms from 2-PrOH; mp 208–210°C; IR (KBr): 3260 (OH), 1660, 1620 (CO); ^{1}H NMR ($CDCl_3$): 4.72 (4H, s, 2×CH_2Ph), 6.94 (1H, dt, *J*=1.3, 6.9 Hz, 7-H), 7.16–7.35 (11H, ov, Ph-H and 9-H), 7.60 (1H, ddd, *J*=1.3, 6.9, 8.6 Hz, 8-H), 8.30 (1H, s, –CH=N–), 9.00 (1H, br d, *J*=6.9 Hz, 6-H), 9.7–10.4 (1H, br, OH); ^{13}C NMR ($CDCl_3$): 53.51, 91.18, 113.46, 124.73, 127.33, 127.85, 128.14, 128.54, 136.82, 137.47, 145.16, 148.75, 156.96, 162.25. Anal. calcd for $C_{23}H_{20}N_4O_2$ (384.4): C, 71.86; H, 5.24; N, 14.57. Found: C, 71.95; H, 5.26; N, 14.47.

4.2.4. 2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbaldehyde oxime (2d). 81%; Yellow prisms from MeOH; mp 214–216°C; IR (KBr): 3240 (OH), 1660, 1620 (CO); ^{1}H NMR ($CDCl_3$): 1.45 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 4.58 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 7.15 (1H, ddd, *J*=1.3, 6.9, 8.6 Hz, 7-H), 7.51 (1H, ddd, *J*=0.7, 1.3, 6.9 Hz, 9-H), 7.79 (1H, ddd, *J*=1.7, 6.9, 8.6 Hz, 8-H), 8.54 (1H, s, –CH=N–), 9.17 (1H, ddd, *J*=0.7, 1.7, 6.9 Hz, 6-H), 9.79 (1H, br, OH); ^{13}C NMR ($CDCl_3$): 14.67, 63.40, 92.02, 115.17, 124.89, 128.70, 137.75, 143.58, 149.56, 155.90, 165.17. Anal. calcd for $C_{11}H_{12}N_3O_3$ (233.3): C, 56.65; H, 4.75; N, 18.02. Found: C, 56.58; H, 4.81; N, 17.95.

4.3. General procedures for the reaction of oximes 2 with NPMI (3)

The solution of oxime **2a** (0.26 g, 1.0 mmol) and NPMI (**3**: 0.19 g, 1.1 mmol) in benzene (3 mL) was heated under reflux for 36 h. After cooling, the resulting crystals (**4a**: 0.29 g, 71%) were filtered off. The filtrate was evaporated to dryness, which was subjected to a column chromatography on silica gel to afford **4a** (0.045 g, 11%) and the unreacted oxime **2a** (0.018 g, 7%) with hexane/ethyl acetate (1:1) as an eluent.

4.3.1. (3*R,3a*S**,6a*S**)-(±)-3-[4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (4a).** Colorless needles from ethanol; mp 224°C; IR (KBr): 3200 (NH), 1730, 1710, 1620 (CO); ^{1}H NMR ($CDCl_3$): 1.96 [4H, br, $N(CH_2CH_2)_2$], 3.73 [2H, m, $N(CHHCH_2)_2$], 3.80 [3H, ov, 3a-H and $N(CHHCH_2)_2$], 4.97 (1H, dd, *J*=8.9, 12.9 Hz, 3-H), 5.28 (1H, d, *J*=7.9 Hz, 6a-H), 6.83 (1H, *J*=1.3, 6.9, 8.6 Hz, 7′-H), 7.26 (1H, *J*=0.7, 1.3, 6.9 Hz, 9′-H), 7.38–7.58 (6H, ov, 8′-H and Ph-H), 7.83 (1H, d, *J*=12.9 Hz, exchanged with D_2O, NH), 8.64 (1H, *J*=0.7, 1.7, 6.9 Hz, 6′-H); ^{13}C [$(CD_3)_2SO$]: 25.23, 50.14, 51.94, 62.50, 82.13, 83.83, 113.89, 123.87, 126.36, 127.01, 128.27, 128.74, 132.54, 137.94, 147.89, 157.85, 160.23, 173.21, 174.92. Anal. calcd for $C_{23}H_{21}N_4O_5$ (431.4): C, 64.04; H, 4.91; N, 16.23. Found: C, 64.17; H, 5.01 N, 16.27.

While the reaction of oximes **2b** and **2c** with NPMI (**3**) and usual work-up with a column chromatography gave (**4b** and **5b**) and (**4c** and **5c**), respectively, the reaction of oxime **2d** with **3** gave **4d**.

4.3.2. (3*R,3a*S**,6a*S**)-(±)-3-(2-Morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (4b).** Colorless needles from 2-PrOH; mp 186–187°C; IR (KBr): 3240 (NH), 1740, 1710, 1630 (CO); ^{1}H NMR ($CDCl_3$): 3.47 [4H, m, $N(CH_2CH_2)_2O$], 3.77–3.85 [5H, ov, 3a-H and $N(CH_2CH_2)_2O$], 4.79 (1H, dd, *J*=9.2, 13.5 Hz, 3-H), 5.31 (1H, d, *J*=7.9 Hz, 6a-H), 7.00 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.39–7.49 (6H, ov, 9′-H and Ph-H), 7.57 (1H, d, *J*=13.5 Hz, exchanged with D_2O, NH), 7.68 (1H, ddd, *J*=1.2, 6.6, 8.3 Hz, 8′-H), 8.72 (1H, ddd, *J*=0.7, 1.2, 6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 50.32, 51.21, 63.97, 66.85, 81.82, 89.27, 114.57, 125.07, 126.72, 126.81, 128.66, 128.97, 132.00,

137.09, 149.07, 159.25, 165.32, 172.74, 174.16. Anal. calcd for $C_{23}H_{21}N_5O_5$ (447.4): C, 61.74; H, 4.73; N, 15.65. Found: C, 61.68; H, 4.79; N, 15.30.

4.3.3. (3*R* *,3a*R* *,6a*R* *)-(±)-3-(2-Morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (5b). Although this compound could not be isolated as a pure form, the structure was elucidated by its ^{1}H NMR spectroscopic data ($CDCl_3$): 3.59 [2H, br, N(C*H*HCH$_2$)$_2$O], 3.71–3.85 [6H, ov, N(CH*H*CH$_2$)$_2$O], 4.52 (1H, dd, *J*=5.9, 7.3 Hz, 3a-H), 4.68 (1H, dd, *J*=5.9, 12.5 Hz, 3-H), 5.33 (1H, d, *J*=7.3 Hz, 6a-H), 6.78 (1H, d, *J*=12.5 Hz, NH), 7.05 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.31–7.53 (6H, ov, 9′-H and Ph-H), 7.72 (1H, ddd, *J*=1.7, 6.9, 8.6 Hz, 8′-H), 8.85 (1H, ddd, *J*=0.7, 1.7, 6.9 Hz, 6′-H).

4.3.4. (3*R* *,3a*S* *,6a*S* *)-(±)-3-{2-(*N*,*N*-Dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (4c). Colorless needles from 2-PrOH; mp 170°C; IR (KBr): 3200 (NH), 1720, 1660, 1630 (CO); ^{1}H NMR ($CDCl_3$): 3.66 (1H, dd, *J*=7.9, 8.9 Hz, 3a-H), 4.59, 4.77 (each 2H, each d, *J*=15.8 Hz, 2×C*H*$_2$Ph), 4.91 (1H, dd, *J*=8.9, 13.2 Hz, 3-H), 5.15 (1H, d, *J*=7.9 Hz, 6a-H), 6.97 (1H, ddd, *J*=1.0, 6.9, 8.3 Hz, 7′-H), 7.26–7.48 (16H, ov, 9′-H and Ph-H), 7.63 (1H, ddd, *J*=1.7, 6.6, 8.3 Hz, 8′-H), 7.77 (1H, d, *J*=13.2 Hz, exchanged with D_2O, NH), 8.74 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 51.20, 53.68, 63.83, 81.76, 88.52, 114.12, 124.85, 126.76, 126.86, 127.48, 127.80, 128.63, 128.73, 128.97, 132.02, 136.93, 137.11, 148.48, 159.17, 165.21, 172.87, 174.32. Anal. calcd for $C_{33}H_{27}N_5O_4$ (557.6): C, 71.08; H, 4.88; N, 12.56. Found: C, 70.83; H, 5.10; N, 12.51.

4.3.5. (3*R* *,3a*R* *,6a*R* *)-(±)-3-{2-(*N*,*N*-Dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (5c). Colorless needles from 2-PrOH; mp 119–120°C; IR (KBr): 3210 (NH), 1720, 1650, 1620 (CO); ^{1}H NMR ($CDCl_3$): 4.54 (1H, dd, *J*=6.6, 7.9 Hz, 3a-H), 4.73 (3H, ov, 3-H and 2×C*H*HPh), 4.89 (2H, d, *J*=16.2 Hz, 2×CH*H*Ph), 5.24 (1H, d, *J*=7.9 Hz, 6a-H), 6.96 (1H, br t, *J*=6.9 Hz, 7′-H), 7.13–7.49 (17H, ov, 9′-H and Ph-H and NH), 7.62 (1H, br dd, *J*=6.9, 7.3 Hz, 8′-H), 8.82 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 52.85, 53.07, 64.15, 82.75, 88.39, 113.71, 124.85, 126.54, 127.17, 127.53, 128.25, 128.59, 128.70, 128.95, 131.14, 136.96, 137.30, 148.63, 158.76, 163.99, 170.48, 174.81. HRMS (EI) *m/z*: 557.2045 (calcd for $C_{33}H_{27}N_5O_4$: 557.2063). Anal. calcd for $C_{33}H_{27}N_5O_4$ (557.6): C, 71.08; H, 4.88; N, 12.56. Found: C, 70.53; H, 5.10 N, 12.51.

4.3.6. (3*R* *,3a*S* *,6a*S* *)-(±)-3-(2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)-5-phenylperhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (4d). Colorless crystals without recrystallization; mp 181–182°C; IR (KBr): 3200 (NH), 1700, 1660, 1620 (CO); ^{1}H NMR ($CDCl_3$): 1.43 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 3.83 (1H, dd, *J*=7.6, 8.9 Hz, 3a-H), 4.55 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.17 (1H, dd, *J*=8.9, 13.5 Hz, 3-H), 5.29 (1H, d, *J*=7.6 Hz, 6a-H), 7.13 (1H, ddd, *J*=1.0, 6.9, 8.3 Hz, 7′-H), 7.35–7.51 (6H, ov, 9′-H and Ph-H), 7.71–7.80 (2H, ov, 8′-H and NH), 8.89 (1H, br d, *J*=6.9 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 14.63, 51.43, 60.77, 63.12, 81.42, 87.82, 115.27, 124.91, 126.69, 127.37, 128.30, 128.70, 129.00, 131.84, 134.17, 137.66, 149.90, 158.42, 165.86, 172.88, 173.94. Anal. calcd for $C_{21}H_{18}N_4O_5$ (406.4): C, 62.06; H, 4.46; N, 13.79. Found: C, 62.16; H, 4.48; N, 13.62.

Similarly, the reaction of oxime **2a** with **7** gave **8** and **9** in 68 and 4% yields, respectively.

4.3.7. (3*R* *,3a*S* *,6a*S* *)-(±)-5-Methyl-3-{4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}perhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (8). Colorless crystals without recrystallization; mp 200–201°C; IR (KBr): 3190 (NH), 1710, 1700, 1640 (CO); ^{1}H NMR ($CDCl_3$): 1.96 [4H, br, N(CH$_2$C*H*$_2$)$_2$], 3.04 (3H, s, 5-Me), 3.61 (1H, dd, *J*=7.3, 8.9 Hz, 3a-H), 3.68, 3.77 [each 2H, each m, N(C*H*$_2$CH$_2$)$_2$], 4.86 (1H, dd, *J*=8.9, 12.5 Hz, 3-H), 5.12 (1H, d, *J*=7.3 Hz, 6a-H), 6.83 (1H, *J*=1.7, 6.9, 7.3 Hz, 7′-H), 7.27 (1H, *J*=1.0, 1.7, 8.9 Hz, 9′-H), 7.55 (2H, ov, 8′-H and NH), 8.61 (1H, ddd, *J*=1.0, 7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 25.23, 25.70, 50.46, 51.57, 63.63, 81.98, 83.85, 112.65, 124.35, 126.72, 136.39, 148.46, 158.51, 161.13, 174.14, 175.35. Anal. calcd for $C_{18}H_{19}N_5O_4$ (369.4): C, 58.53; H, 5.18; N, 18.96. Found: C, 58.77; H, 5.30; N, 18.78.

4.3.8. (3*R* *,3a*R* *,6a*R* *)-(±)-5-Methyl-3-{4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl}perhydropyrrolo[3,4-*d*]isoxazole-4,6-dione (9). Colorless needles from 2-PrOH; mp 202–203°C; IR (KBr): 3180 (NH), 1690, 1640, 1620 (CO); ^{1}H NMR ($CDCl_3$): 1.85, 1.98 [each 2H, each m, N(CH$_2$C*H*$_2$)$_2$], 3.01 (3H, s, 5-Me), 3.77 [4H, m, N(C*H*$_2$CH$_2$)$_2$], 4.45 (1H, dd, *J*=5.9, 7.3 Hz, 3a-H), 4.80 (1H, dd, *J*=5.9, 12.5 Hz, 3-H), 5.20 (1H, d, *J*=7.3 Hz, 6a-H), 6.81 (1H, d, *J*=12.5 Hz, NH), 6.87 (1H, ddd, *J*=1.5, 6.9, 7.3 Hz, 7′-H), 7.28 (1H, ddd, *J*=0.6, 1.5, 8.9 Hz, 9′-H), 7.59 (1H, br dd, *J*=6.9, 8.9 Hz, 8′-H), 8.74 (1H, dd, *J*=0.6, 7.3 Hz, 6′-H); ^{13}C NMR ($CDCl_3$): 24.92, 25.66, 50.57, 53.69, 63.32, 83.22, 86.21, 112.63, 124.58, 126.49, 136.51, 148.71, 158.29, 159.04, 171.87, 177.00. Anal. calcd for $C_{18}H_{19}N_5O_4$ (369.4): C, 58.53; H, 5.18; N, 18.96. Found: C, 58.23; H, 5.22; N, 18.67.

4.4. Reaction of oximes 2 with electron-deficient acetylenes 10, 16, and 17

General procedures for the reaction of oximes **2** *with DMAD* (**10**). A solution of oxime **2a** (0.135 g, 0.52 mmol) and DMAD (**10**; 0.066 mL, 1.0 equiv.) in benzene (3 mL) was heated under reflux for 2 h. The solvent was evaporated to dryness, which was subjected to a column chromatography on silica gel to afford **11a** (0.173 g, 84%) and **12a** (trace) with hexane/ethyl acetate (1:2) and (2:3) as eluents, respectively.

4.4.1. 3-Oxo-2-{3-[4-oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]aminomethylene}succinic acid dimethyl ester (11a). Pale yellow needles from 2-PrOH; mp 205°C; IR (KBr): 3120 (NH), 1740, 1700, 1660 (CO); ^{1}H NMR ($CDCl_3$): 1.96 [4H, br, N(CH$_2$C*H*$_2$)$_2$], 3.76 [4H, br, N(C*H*$_2$CH$_2$)$_2$], 3.80, 3.92 (each 3H, each s, OMe), 6.94 (1H, dt, *J*=1.3, 6.9 Hz, 7′-H), 7.31 (1H, br d, *J*=8.9 Hz, 9′-H), 7.61 (1H, ddd, *J*=1.7, 6.9, 8.9 Hz, 8′-H), 8.83–8.56 (2H, ov, 6′-H and –NH–C*H*=), 11.81 (1H, d,

J=13.9 Hz, exchanged with D_2O, –N*H*–CH═); ^{13}C NMR ($CDCl_3$): 25.47, 49.81, 51.43, 52.31, 97.65, 97.84, 113.17, 124.40, 127.64, 136.51, 147.89, 153.84, 154.93, 160.27, 165.93, 166.31, 186.88. Anal. calcd for $C_{19}H_{20}N_4O_6$ (400.4): C, 56.99; H, 5.04; N, 13.99. Found: C, 56.78; H, 5.11; N, 14.08.

4.4.2. 4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (12a). Colorless prisms from 2-PrOH; mp 250–251°C; IR (KBr): 2200 (CN), 1670 (CO); ^1H NMR ($CDCl_3$): 2.00 [4H, br, N(CH_2CH_2)$_2$], 3.90 [4H, br, N(CH_2CH_2)$_2$], 6.87 (1H, ddd, J=1.0, 6.6, 7.3 Hz, 7-H), 7.24 (1H, br d, J=8.6 Hz, 9-H), 7.64 (1H, ddd, J=1.7, 6.6, 8.6 Hz, 8-H), 8.80 (1H, br d, J=7.3 Hz, 6-H). Anal. calcd for $C_{13}H_{12}N_4O$ (240.3): C, 64.99; H, 5.03; N; 23.32. Found: C, 64.73; H, 5.07; N, 23.24.

4.4.3. 3-Oxo-2-{3-(2-morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)aminomethylene}succinic acid dimethyl ester (11b). Yellow prisms from MeOH; mp 212°C; IR (KBr): 3100 (NH), 1740, 1705, 1660 (CO); ^1H NMR ($CDCl_3$): 3.45 [4H, t, J=4.6 Hz, N(CH_2CH_2)$_2$O], 3.79 (3H, s, OMe), 3.90 [7H, ov, N(CH_2CH_2)$_2$O and OMe], 7.14 (1H, ddd, J=1.3, 6.6, 7.3 Hz, 7′-H), 7.52 (1H, br d, J=8.9 Hz, 9′-H), 7.74 (1H, ddd, J=1.7, 6.6, 8.9 Hz, 8′-H), 8.99 (1H, ddd, J=1.0, 1.7, 7.3 Hz, 6′-H), 9.65 (1H, d, J=13.5 Hz, –NH–C*H*═), 12.32 (1H, d, J=13.5 Hz, –N*H*–CH═); ^{13}C ($CDCl_3$): 48.97. 51.52, 52.23, 66.54, 98.13, 102.91, 115.15, 125.34, 127.33, 136.42, 147.19, 153.67, 156.08, 157.57, 165.79, 166.25, 186.85. Anal. calcd for $C_{19}H_{20}N_4O_7$ (416.4): C, 54.81; H, 4.84; N, 13.46. Found: C, 54.41; H, 4.87; N, 13.20.

4.4.4. 2-Morpholino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (12b). Colorless prisms from 2-PrOH; mp 180°C; IR (KBr): 2200 (CN), 1680 (CO); ^1H NMR ($CDCl_3$): 3.81 [4H, t, J=4.6 Hz, N(CH_2CH_2)$_2$O], 4.06 [4H,t, J=4.6 Hz, N(CH_2CH_2)$_2$O], 6.69 (1H, ddd, J=1.7, 6.6, 7.3 Hz, 7-H), 7.30 (1H, br d, J=8.6 Hz, 9-H), 7.73 (1H, ddd, J=1.7, 6.6, 8.6 Hz, 8-H), 8.84 (1H, ddd, J=1.0, 1.7, 7.3 Hz, 6-H). Anal. calcd for $C_{13}H_{12}N_4O_2$ (256.3): C, 60.93; H, 4.72; N, 21.86. Found: C, 60.68; H, 4.85; N, 21.87.

4.4.5. 3-Oxo-2-{3-[2-(*N*,*N*-dibenzylamino)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]aminomethylene}succinic acid dimethyl ester (11c). Yellow prisms from 2-PrOH; mp 158–159°C; IR (KBr): 3120 (NH), 1740, 1700, 1660 (CO); ^1H NMR ($CDCl_3$): 3.71, 3.91 (each 3H, each s, OMe), 4.77 (4H, s, 2×CH_2Ph), 7.04 (1H, ddd, J=1.3, 6.6, 7.3 Hz, 7′-H), 7.18–7.33 (10H, ov, Ph-H), 7.43 (1H, br d, J=8.6 Hz, 9′-H), 7.68 (1H, ddd, J=1.7, 6.6, 8.6 Hz, 8′-H), 8.65 (1H, d, J=13.5 Hz, –NH–C*H*═), 8.87 (1H, ddd, J=0.6, 1.3, 7.3 Hz, 6′-H), 11.94 (1H, d, J=13.5 Hz, –N*H*–CH═); ^{13}C NMR ($CDCl_3$): 51.36, 52.29, 53.73, 98.08, 101.18, 114.27, 125.01, 127.46, 127.51, 127.58, 128.73, 136.64, 136.98, 147.42, 155.18, 156.13, 159.30, 165.84, 166.13, 186.97. Anal. calcd for $C_{29}H_{26}N_4O_6$ (526.5): C, 66.15; H, 4.98; N, 10.64. Found: C, 66.19; H, 5.05; N, 10.56.

4.4.6. 2-(*N*,*N*-Dibenzyl)amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (12c). Colorless needles from 2-PrOH; mp 180°C; IR (KBr): 2200 (CN), 1680 (CO); ^1H NMR ($CDCl_3$): 5.07 (4H, s, 2×CH_2Ph), 6.97 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.24–7.39 (11H, ov, 9-H and Ph-H), 7.70 (1H, ddd, J=1.7, 6.9, 8.9 Hz, 8-H), 8.85 (1H, ddd, J=0.7, 1.7, 6.9 Hz, 6-H). Anal. calcd for $C_{23}H_{18}N_4O$ (366.4): C, 75.36; H, 4.95; N, 15.29. Found: C, 75.25; H, 5.10; N, 15.12.

4.4.7. 3-Oxo-2-{3-[2-ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]aminomethylene}succinic acid dimethyl ester (11d). Pale yellow needles from 2-PrOH; mp 181°C; IR (KBr): 3200 (NH), 1740, 1700, 1680 (CO); ^1H NMR ($CDCl_3$): 1.53 (3H, t, J=6.9 Hz, OCH_2CH_3), 3.80. 3.92 (each 3H, each s, OMe), 4.65 (2H, q, J=6.9 Hz, OCH_2CH_3), 7.26 (1H, ddd, J=1.0, 6.9, 7.3 Hz, 7′-H), 7.60 (1H, br d, J=7.3 Hz, 9′-H), 7.83 (1H, ddd, J=1.0, 6.9, 7.3 Hz, 8′-H), 9.10 (1H, br d, J=7.3 Hz, 6′-H), 9.70 (1H, d, J=13.5 Hz, –NH–C*H*═), 12.67 (1H,d, J=13.5 Hz, –N*H*–CH═); ^{13}C NMR ($CDCl_3$): 14.59, 51.47, 52.26, 64.33, 98.06, 100.72, 115.90, 125.05, 127.55, 136.82, 146.85, 152.38, 154.73, 157.83, 165.95, 166.50, 186.58; MS (EI) *m*/*z*: 375 (M^+, 27), 316 (100). Anal. calcd for $C_{17}H_{17}N_3O_7$ (375.3): C, 54.40; H, 4.57; N, 11.20. Found: C, 54.27; H, 4.66; N, 10.92.

4.4.8. 2-Ethoxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbonitrile (12d). Colorless needles from 2-PrOH; mp 153°C; IR (KBr): 2220 (CN), 1670 (CO); ^1H NMR ($CDCl_3$): 1.46 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.60 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.32 (1H, dt, J=1.3, 6.9 Hz, 7-H), 7.61 (1H, br d, J=8.6 Hz, 9-H), 8.03 (1H, ddd, J=1.7, 6.9, 8.6 Hz, 8-H), 9.00 (1H, ddd, J=1.0, 1.7, 6.9 Hz, 6-H). Anal. calcd for $C_{11}H_9N_3O_2$ (215.2): C, 61.39; H, 4.22; N, 19.53. Found: C, 61.32; H, 4.19; N, 19.09.

Similarly, the reaction of oxime **2a** with acetylenes **16** and **17** gave (**18** and **12a**) and (**19** and **12a**), respectively.

4.4.9. 2-{3-[4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]aminomethylene}-1,4-diphenylbutane-1,2,4-trione (18). Yellow prisms from benzene; mp 232–233°C; this compound was obtained as a (1:1) molecular complex with benzene. Anal. calcd for $C_{35}H_{30}N_4O_4$ ($C_{29}H_{24}N_4O_4$+C_6H_6: 570.6): C, 73.67; H, 5.30; N, 9.82. Found: C, 73.79; H, 5.30; N, 9.82; IR (KBr): 3220 (NH), 1660, 1620; ^1H ($CDCl_3$): 1.98 [4H, br, N(CH_2CH_2)$_2$], 3.74 [4H, br, N(CH_2CH_2)$_2$], 6.91 (1H, ddd, J=1.3, 6.9, 7.3 Hz, 7′-H), 7.23–7.63 (8H, ov, 8′- and 9′-H and Ph-H), 7.73 (2H, dd, J=1.7, 7.9 Hz, Ph-H), 7.92 (2H, dd, J=0.7, 8.2 Hz, Ph-H), 8.55 (1H, d, J=13.2 Hz, –NH–C*H*═), 8.70 (1H, dd, J=0.7, 7.3 Hz, 6′-H), 12.09 (1H, d, J=13.2 Hz, –N*H*–CH═); ^{13}C NMR ($CDCl_3$): 25.53, 49.85, 98.06, 109.06, 113.12, 124.45, 127.65, 127.99, 128.57, 129.25, 129.36, 131.57, 133.21, 133.92, 136.49, 137.97, 147.87, 153.91, 155.04, 161.18, 192.67, 193.17, 197.16.

4.4.10. 2-{3-[4-Oxo-2-(pyrrolidin-1-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]aminomethylene}malonaldehydric acid methyl ester (19). Pale yellow needles from benzene; mp 231–232°C; IR (KBr): 3100 (NH), 1700, 1650, 1630 (CO); ^1H NMR ($CDCl_3$): 1.95 [4H, br, N(CH_2CH_2)$_2$], 3.65–3.85 [7H, ov, N(CH_2CH_2)$_2$ and OMe], 6.92 (1H, dt, J=1.3, 6.6 Hz, 7′-H), 7.30 (1H, br d, J=8.3 Hz, 9′-H), 7.61 (1H, ddd, J=1.7, 6.6, 8.3 Hz, 8′-H), 8.53 (1H, dd, J=3.6, 13.5 Hz, –NH–C*H*═), 8.84 (1H, ddd, J=0.7, 1.7, 6.6 Hz,

6′-H), 9.93 (1H, d, J=3.6 Hz, –CHO), 11.90 (1H, d, J=13.5 Hz, –N*H*–CH=); ^{13}C NMR ($CDCl_3$): 25.43, 49.63, 51.04, 98.08, 101.56, 112.96, 124.35, 127.76, 136.28, 147.85, 154.03, 155.24, 158.78, 167.58, 191.10. Anal. calcd for $C_{17}H_{18}N_4O_4$ (342.4): C, 59.64; H, 5.30; N, 16.37. Found: C, 59.46; H, 5.41; N, 16.30.

4.5. General procedures for the preparation of nitriles 12 from aldehydes 1

To a solution cooled at 5°C of aldehyde **1a** (1.00 g, 4.1 mmol) in water (5 mL), hydroxylamine *O*-sulfonic acid (HOS in 81% purity: 0.75 g, 1.3 equiv.) was added. The reaction mixture was stirred at the same temperature for 1 h, heated at 50°C for 3 h, and made basic (pH 8.05) with 1N NaOH. The mixture was extracted with dichloromethane (3×10 mL). The organic layer was dried and the solvent was evaporated to afford nitrile **12a** (0.836 g, 85%). Similarly, nitriles **12b–d** were obtained from aldehydes **1b–d** in 70–89% yields.

4.6. Alkaline hydrolysis of 11a

A solution of **11a** (0.080 g, 0.18 mmol) in 1N NaOH (2 mL) was stirred at room temperature for 1 h. The reaction mixture was extracted with dichloromethane (20 mL×2). The organic layer was dried and the solvent was evaporated. The residue was subjected to a column chromatography on silica gel to afford **13** (0.034 g, 80%) with dicholoromethane/MeOH (25:1) as an eluent.

4.6.1. 3-Amino-2-(pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (13). Yellow prisms from 2-PrOH; mp 122°C; ^{1}H NMR ($CDCl_3$): 1.95 [4H, br, N(CH_2CH_2)$_2$], 3.0–3.7 (2H, br, NH_2), 3.79 [4H, br, N(CH_2CH_2)$_2$], 6.86 (1H, dt, J=1.5, 6.8 Hz, 7-H), 7.29 (1H, dd, J=1.0, 7.8 Hz, 9-H), 7.39 (1H, m, 8-H), 8.83 (1H, dd, J=1.0, 6.4 Hz, 6-H); ^{13}C NMR ($CDCl_3$): 25.5, 48.8, 108.5, 112.7, 124.2, 126.6, 131.8, 143.1, 150.6, 153.6; MS (FAB) *m/z*: 230 (M^+). Anal. calcd for $C_{12}H_{14}N_4O$ (230.3): C, 62.59; H, 6.13; N, 24.33. Found: C, 62.55; H, 6.19; N, 24.28. HRMS (EI) *m/z*: 230.1147 (calcd for $C_{12}H_{14}N_4O$: 230.1168).

4.7. Single-crystal X-ray structure determination of 13[6]

Single crystals (prisms) of compound **13** for X-ray diffraction studies were obtained by recrystallization from 2-PrOH (crystal of approximate dimensions, 0.16×0.38×0.72 mm^3). All measurements were made on a Rigaku AFC55 diffractometer by employing graphite-monochromated Mo Kα radiation. The unit-cell dimensions were obtained by least-squares analysis of 22 reflections within the range of $25.64<2\theta<27.78°$. The crystal data for **13** are given: crystal system: monoclinic; space group: $P2_1/c$ (#14); cell constants: a: 15.008(7) Å, b: 4.823(5) Å, c: 16.351(5) Å, V: 1085(1) Å^3, β: 113.51(2)°; Z value: 4; D_c: 1.41 g cm^{-3}. The ω–2θ scan technique to a maximum 2θ-value of 55.0° was used and scans of $(1.63+0.30 \tan \theta)°$ were made at a speed of 16° min^{-1} **13**. A total of 2896 observed reflections (unique: 2794; R_{int}=0.020) was collected. All calculations were performed using TEXAN program.[7] Atoms other than hydrogen were refined anisotropically. The structure of compound **13** was solved by direct method (SIR88)[8] and refined by least-squares to R 0.059 (R_w 0.051).

4.8. Preparation of 11a by the reaction of 13 and 15

A mixture of 2-oxosuccinic acid dimethyl ester (**14**: 7.77 g, 48.5 mmol), prepared accordingly to the literature by Sucrow and Grosz,[9] triethyl orthoformate (7.19 g, 1.0 equiv.), and acetic anhydride (9.90 g, 2 equiv.) was stirred at 100°C for 1 h. The reaction mixture was evaporated in vacuo to afford 2-ethoxymethylene-3-oxo-succinic acid dimethyl ester (**15**: 9.77 g, 93%). Ester **15** was used for the next reaction without further purification.

4.8.1. 2-Ethoxymethylene-3-oxosuccinic acid dimethyl ester (15). Colorless oil. This compound was obtained as a (1:1) mixture of two diastereomers. ^{1}H NMR ($CDCl_3$): 1.46, 1.44 (each 3H, each t, J=7.1 Hz, OCH_2CH_3), 3.77, 3.79, 3.87, 3.88 (each 3H, each s, OMe), 4.35, 4.39 (each 2H, q, J=7.1 Hz, OCH_2CH_3), 7.93, 7.95 (each 1H, each s, =C*H*–OEt). HRMS (EI) *m/z* 216.0584 (calcd for $C_{12}H_{14}N_4O$: 216.0634).

To a stirred solution of 3-amino-2-(pyrrolidin-1-yl)pyrido[1,2-*a*]pyrimidin-4(4*H*)-one (**13**: 0.046 g, 0.20 mmol) in THF (0.5 mL), ester **15** (0.058 g, 0.27 mmol) was added at room temperature. The mixture was stirred for 1 h and the solvent was evaporated. The residue was subjected to a preparative TLC with dichloromethane/MeOH (25:1) as an eluent to afford the desired **11a** (0.064 g, 80%).

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