Reactivity of Thioaldehyde: Cyclization Reaction of 6-Amino-1,3-dimethyl-5-thioformyluracil with Enamines into Pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones

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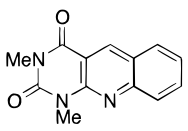
Until quite recently investigation of the chemical properties of monomeric thioaldehydes was considered difficult because of their extreme instability.[1] Although two types of stable monomeric thioaldehydes are known in literature to be kinetically stabilized[2,3] or thermodynamically stabilized compounds,[4,5] only a few reports have appeared concerning the reactivities of stable thioaldehydes.[3,5,6] We recently reported[5c] the synthesis and reactivities of 6-amino-5-thioformyluracils (*e.g.*, **1**) which are kinetically stabilized by the mesomeric effect of the 6-amino group. In order to gain further understanding of the reactivity of the thioformyluracils, we have evaluated the reactions of 6-amino-1,3-dimethyl-5-thioformyluracil (**1**) with enamines.

In our initial study, the thioaldehyde **1** reacted with morpholino enamine **2a** in anhydrous acetonitrile at rt to afford the pyrido[2,3-*d*]pyrimidine derivative **3a** in 75% yield (Table 1). The structure of **3a** was confirmed in the conversion of **3a** into the literature known 5-deazaalloxazine **4**[7] by sulfur oxidation.



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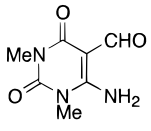

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To establish the generality of this cyclization, the thioaldehyde **1** was subjected to analogous reactions with various morpholino enamines **2b**−**g** in anhydrous acetonitrile. The results are summarized in Table 1. The cyclization proceeded in good yields in the case of enamines **2a**−**d** with aliphatic substituents (R^1 and R^2) (entry 1−4). Most importantly, the cyclization regiospecificity proceeded by use of unsymmetric enamines (entry 3−6). In contrast to the case of the alkyl-substituted enamines **2a**−**d**, the reaction with phenyl-substituted enamines **2e** and **2f** gave a considerable amount of byproduct **5** together with the expected products **3e** and **3f**, respectively (entry 5 and 6). The structure of **5** was presumed to be 1,3-dimethyl-7-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione on the basis of its microanalytical and spectral data. The ultimate proof of the structure was provided by an alternative synthesis of **5** from 6-imino-1,3-dimethyl-5-[(dimethylamino)methylene]-5,6-dihydrouracil hydrochloride (**6**) and 5-carbamoyl-1,3-dimethyluracil (**7**) according to our method.[8] In particular, the cyclization with diphenylenamine **2g** gave only the byproduct **5** in 61% yield (entry 7). In addition, the reaction with less reactive olefins such as methyl acrylate and acrylonitrile resulted in the recovery of the starting material under a variety of thermal or photoreaction conditions. These results indicate that the substitution of the electron-donating groups on enamine is crucial in these cyclization reactions.

On the other hand, the corresponding aldehyde **8** did not react with enamines **2a** and **2b** under the same conditions, and the starting material was recovered even under reflux conditions. As the cycloadditions of uracildienols were achieved only with electron-deficient dienophiles in the literature,[9] the reaction should proceed in

Scheme 1

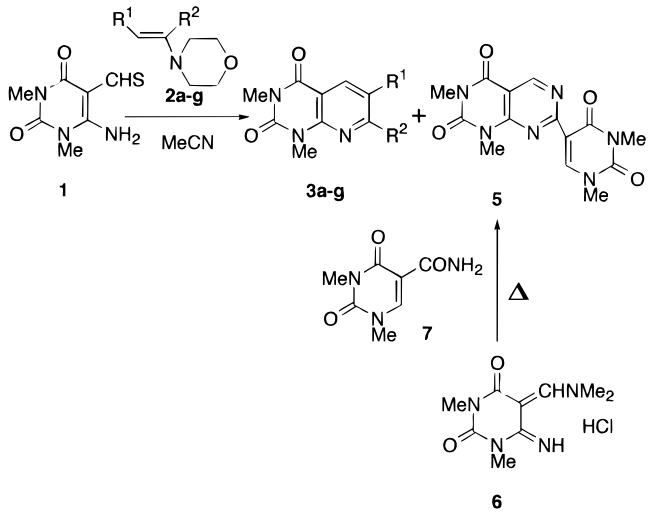

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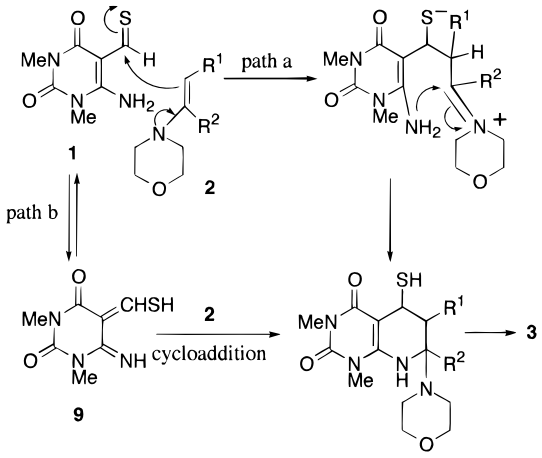
Table 1. Reaction of 6-Amino-1,3-dimethyl-5-thioformyluracil (1) with Enamines 2

				reaction conditions		yield (%)[a]	
entry	enamine	R^1	R^2	temperature	time (h)	**3**	**5**
1	**2a**	$-(CH_2)_4-$		r.t.	5	75	ND
2	**2b**	$-(CH_2)_3-$		r.t.	7	93	ND
3	**2c**	Me	H	r.t.	8	80	ND
4	**2d**	H	Me	r.t.	1	73	ND
5	**2e**	Ph	H	reflux	24	41	35
6	**2f**	Me	Ph	reflux	24	15	61
7	**2g**	Ph	Ph	reflux	16	ND	61

[a] ND: Not detectable.

Scheme 2

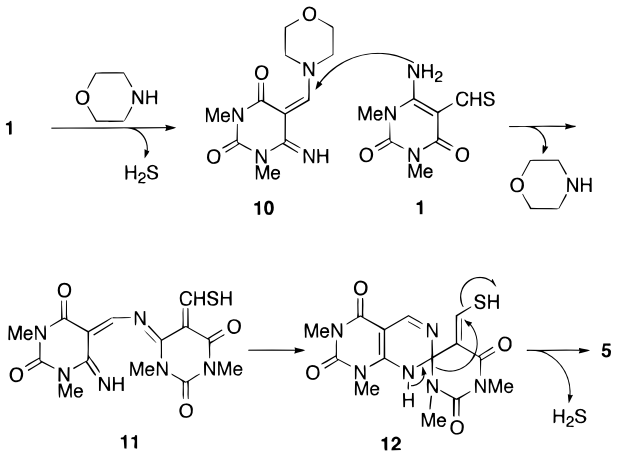


a stepwise manner (path a in Scheme 2). Path a involves a rare example of nucleophilic attack of the electron-rich enamine **2** on the thioformyl group of **1**, which suggests the high reactivity of the thioformyl group. However, taking into consideration that stabilization of the thioformyluracil **1** is ascribed to a tautomerism into 6-imino-5-(mercaptomethylene)uracil structure **9** in solution, a [4 + 2] cycloaddition mechanism (path b) could not be ruled out.[10]

In order to obtain some insight into the mechanistic implications of the formation of **5**, the refluxing of the thioaldehyde **1** in the absence of enamines was carried out under similar conditions. But the starting material was recovered even in the presence of 3 equiv of pyridine as a base. Upon addition of morpholine to the reaction medium, the product **5** was obtained in 62% yield together with the 5-formyluracil **8** (22% yield) which was formed by the hydrolysis of **1** due to slightly contaminated water.[5c] Therefore, morpholine could be required for the self-condensation of **1** as a catalytic secondary amine as depicted in Scheme 3. The intermolecular condensation reaction between the active intermediate **10** and the poorly nucleophilic 6-amino group of **1** and subsequent 6π cyclization of **11** are key reactions to give the spiro-intermediate **12**, which is converted into **5** *via* the ring transformation process.

In conclusion, we have shown that cyclization reactions of 6-amino-5-thioformyluracil **1** with electron-rich enamines **2** under mild conditions are applicable to the regiospecific synthesis of pyrido[2,3-*d*]pyrimidine derivatives **3**. The reactivity can be reduced by the placement of phenyl groups on the enamine. The formation of **3** and **5** suggests that the 5-thioformyl group of **1** possesses much higher reactivity toward nucleophiles compared with the corresponding 5-formyl group of **8**.

Scheme 3



Experimental Section

General.[5c] Acetonitrile was distilled over P_2O_5 immediately prior to use. All reactions involving enamine were carried out under a dry argon atmosphere.

General Procedure for the Preparation of Pyrido[2,3-*d*]pyrimidine derivatives 3a−d. A solution of 6-amino-1,3-dimethyl-5-thioformyluracil (**1**) (1 equiv) and morpholino enamine **2a**−**d** (1.1 equiv) in anhydrous acetonitrile (5 mL/mmol) was stirred at appropriate reaction conditions (see Table 1). The progress of the reaction was monitored by TLC. Acetonitrile was removed *in vacuo*, and the residue was taken up with ether (10 mL). The resulting precipitate was recrystallized from an appropriate solvent to give the pure pyrido[2,3-*d*]pyrimidine **3a**−**d**.

1,3-Dimethyl-6,7,8,9-tetrahydroquinolino[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3a): recrystallized from EtOH−ether, 75%, mp 132−3 °C; UV (EtOH) λ_{max} 312 nm ($\epsilon = 0.89 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 245 (M^+); ^{1}H NMR δ 1.92 (m, 4 H), 2.92 (m, 4 H), 3.49 (s, 3 H), 3.70 (s, 3 H), 8.13 (s, 1 H). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.44; H, 6.27; N, 17.17.

1,3-Dimethylcyclopenta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3b): recrystallized from EtOH, 93%, mp 168−70 °C; UV (EtOH) λ_{max} 320 nm ($\epsilon = 0.96 \times 10^4$ L/mol cm), 252 nm ($\epsilon = 0.85 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 231 (M^+); ^{1}H NMR δ 2.19 (m, 2 H), 3.03 (m, 4 H), 3.46 (s, 3 H), 3.70 (s, 3 H), 8.20 (s, 1 H). Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.26; H, 5.75; N, 18.15.

1,3,6-Trimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3c): recrystallized from EtOH, 80%, mp 163−5 °C (lit.[11] mp 159 °C); UV (MeOH) λ_{max} 317 nm ($\epsilon = 0.55 \times 10^4$ L/mol cm), 249 nm ($\epsilon = 0.71 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 205 (M^+); ^{1}H NMR δ 2.42 (s, 3 H), 3.48 (s, 3 H), 3.71 (s, 3 H), 8.26 (br, 1 H). 8.50 (brd, 1 H, J = 3.0 Hz). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.15; H, 5.30; N, 20.78.

1,3,7-Trimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (3d): recrystallized from ligroin, 73%, mp 160−1 °C (lit.[11] mp 157−8 °C); UV (EtOH) λ_{max} 308 nm ($\epsilon = 0.75 \times 10^4$ L/mol cm), 247 nm ($\epsilon = 0.61 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 205 (M^+); ^{1}H NMR δ 2.62 (s, 3 H), 3.47 (s, 3 H), 3.72 (s, 3 H), 7.08 (d, 1 H, J = 8.0 Hz), 8.39 (d, 1 H, J = 8.0 Hz). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.29; H, 5.35; N, 20.22.

Reaction of the 5-Thioformyluracil 1 with *trans*-1-Morpholino-2-phenylethene (2e). A solution of **1** (400 mg, 2.0 mmol) and **2e** (340 mg, 2.2 mmol) in anhydrous acetonitrile (10 ml) was refluxed for 24 h. The resulting precipitate was collected by filtration and recrystallized from water to give 1,3-dimethyl-7-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**5**) (120 mg, 35%): mp >300 °C; UV (EtOH) insoluble; MS (EI$^+$) *m*/*z* 330 (M^+); ^{1}H NMR (CF_3CO_2H) δ 3.68 (s, 6 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 9.26 (s, 1 H), 9.50 (s, 1 H). Anal. Calcd for $C_{14}H_{14}N_6O_4$: C, 50.91; H, 4.27; N, 25.45. Found: C, 51.01; H, 4.20; N, 25.52.

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The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$ as eluent) and recrystallized from water to give 1,3-dimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3e**) (220 mg, 41%): mp 166−8 °C; UV (EtOH) λ_{max} 328 nm ($\epsilon = 0.51 \times 10^4$ L/mol cm), 271 nm ($\epsilon = 2.38 \times 10^4$ L/mol cm), 228 nm ($\epsilon = 2.20 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 267 (M$^+$); ^{1}H NMR δ 3.50 (s, 3 H), 3.75 (s, 3 H), 7.52 (m, 5 H), 8.65 (d, 1 H, $J = 3$ Hz), 8.92 (d, 1 H, $J = 3$ Hz). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.14; H, 4.94; N, 15.61.

Reaction of the 5-Thioformyluracil 1 with 1-Morpholino-1-phenylpropene (2f). A solution of **1** (200 mg, 1.0 mmol) and **2f** (224 mg, 1.1 mmol) in anhydrous acetonitrile (5 ml) was refluxed for 24 h. The resulting precipitate was collected by filtration and recrystallized from water to give **5** (100 mg, 61%), which was identical with the sample prepared above.

The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$ as eluent) and recrystallized from water to give 7-phenyl-1,3,6-trimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3f**) (43 mg, 15%): mp 175 °C; UV (EtOH) λ_{max} 330 nm ($\epsilon = 1.21 \times 10^4$ L/mol cm), 247 nm ($\epsilon = 1.55 \times 10^4$ L/mol cm); MS (EI$^+$) *m*/*z* 281 (M$^+$); ^{1}H NMR δ 2.44 (brs, 3 H), 3.48 (s, 3 H), 3.70 (s, 3 H), 7.52 (m, 5 H), 8.25 (brs, 1 H). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.03; H, 5.34; N, 14.78.

Reaction of the 5-Thioformyluracil 1 with 1,2-Diphenyl-1-morpholinoethene (2g). A solution of **1** (200 mg. 1.0 mmol) and **2g** (290 mg, 1.1 mmol) in anhydrous acetonitrile (5 ml) was refluxed for 16 h. The resulting precipitate was collected by filtration and recrystallized from water to give **5** (100 mg, 61%), which was identical with the sample prepared above. The corresponding 1,3-dimethyl-6,7-diphenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3g**) could not be obtained.

Alternative Synthesis of 5. (a) A solution of **1** (200 mg. 1.0 mmol) and morpholine (180 mg, 2.0 mmol) in anhydrous acetonitrile (5 ml) was refluxed for 6 h under argon atmosphere. The resulting precipitate was collected by filtration and recrystallized from water to give **5** (103 mg, 62%), which was identical with the sample prepared above. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$ as eluent) to give 6-amino-5-formyl-1,3-dimethyluracil (**8**) (40 mg, 22%), which was identical with an authentic sample.[8]

(b) A mixture of 6-imino-1,3-dimethyl-5-[(dimethylamino)-methylene]-5,6-dihydrouracil hydrochloride (**6**)[8] (123 mg, 0.5 mmol) and 5-carbamoyl-1,3-dimethyluracil (**7**)[12] (183 mg, 1.0 mmol) was heated at 210−20 °C for 2 h. The mixture was taken up with hot EtOH (10 mL), and the resulting precipitate was collected by filtration to give **5** (55 mg, 33%), which was identical with the sample prepared above. After cooling the filtrate, the resulting precipitate was collected by filtration to give recovered **7** (80 mg, 44%).

5-Deaza-1,3-dimethylalloxazine (4). A mixture of **3a** (1.23 g, 5.0 mmol) and sulfur (1.50 g, 47.0 mmol) in quinoline (15 mL) was refluxed for 24 h, and the mixture was then poured into dilute HCl (50 mL). The resulting precipitate was collected by filtration and recrystallized from AcOH to give the 5-deazaalloxazine **4** (0.52 g, 43%), which was identical with an authentic sample.[7]

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