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Reactivities of 6-Amino-1,3-dimethyl-5-thioformyluracil toward Nucleophiles and Its Application to Synthesis of Pyrido[2,3-*d*]pyrimidines

Kosaku Hirota,* Keiko Kubo, and Hironao Sajiki

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502, Japan.

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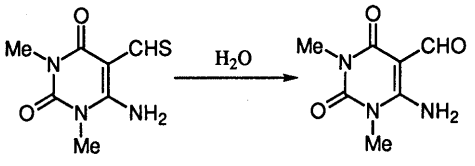
The reaction of the 5-thioformyluracil 1 with phenylhydrazine and various amines readily afforded the hydrazone 3a and Schiff bases 3b—d, respectively. Further, carbanions and Wittig reagents reacted with 1 to give pyrido[2,3-*d*]pyrimidines 4 and 9. The corresponding 5-formyluracil 2 possessed much lower reactivities toward these nucleophiles than did 1.

Key words 5-thioformyluracil; thioaldehyde; aldehyde; nucleophile; pyrido[2,3-*d*]pyrimidine

Simple thioaldehydes are unstable compounds and usually exist as cyclic trimers.[1] The stable monomeric thioaldehydes are classified into two groups: kinetically stabilized[2] by steric protection and thermodynamically stabilized[3—5] by the mesomeric effect through hetero atoms. Recently, we described[5m] the preparation, structure and stability of 5-thioformyluracil derivatives which were stabilized by an amino group at the 6-position. In the study, we found that 6-amino-1,3-dimethyl-5-thioformyluracil (**1**) was subject to nucleophilic attack by water to afford the corresponding aldehyde **2** (Chart 1). There have been few studies on the reactions of stable thioaldehydes with nucleophiles.[2g,5l] We have therefore studied the reactivity of the thioaldehyde **1** with nucleophiles such as hydrazine, amines and carbanions (active methylene compounds and Wittig reagents) for comparison with that of the corresponding aldehyde **2**.

When the thioaldehyde **1** was mixed with 3 mol eq of phenylhydrazine or hydroxylamine in EtOH at room temperature, the corresponding hydrazone **3a** or oxime **3b** was precipitated instantaneously in excellent yield. In addition, the reaction with methylamine and aniline at room temperature proceeded smoothly to afford the Schiff bases **3c** and **3d** in high yields.[6] Although the reaction of the corresponding aldehyde **2**[7] with the same hydrazine and amines gave the same products **3a—d**, the reactions were much slower and the yields became lower (Table 1). The reaction of **2** with aniline required heating under reflux for 24 h (50% yield). It may thus be concluded that the reactivity of the thioaldehyde **1** to amines is considerably enhanced compared to that of the corresponding aldehyde **2**.

The thioaldehyde **1** was treated with active methylene or methyl compounds in the presence of base. As shown in Table 2, the thioaldehyde **1** reacted with malononitrile, ethyl cyanoacetate and diethyl malonate at room temperature to afford pyrido[2,3-*d*]pyrimidines **4a—c**[8] in 59—97% yields. The thioaldehyde **1** could be a convenient intermediate for rapid preparation of pyrido[2,3-*d*]pyrimidine derivatives. The thioaldehyde **1** also reacted with nitromethane (neat) under reflux in the presence of triethylamine to give the (*E*)-olefin **5** in 27% yield together with the isothiazolopyrimidine **6**[5m] in 25% yield. The product **6** is presumably formed via air oxidation of **1**. On the other hand, the corresponding aldehyde **2** did not react with these active methylene compounds under the same conditions, and the starting material was recovered even under reflux.[9]

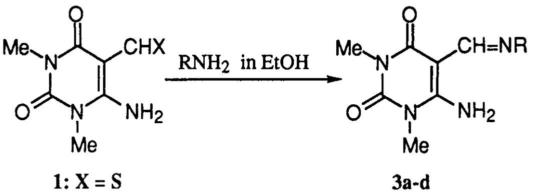


1 **2**

Chart 1

When (carbethoxymethylene)triphenylphosphorane was treated with **1** at room temperature for 24 h, the (*E*)-olefin **7**[10a] was obtained in 79% yield. Upon prolonged heating in acetonitrile (24 h) in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), **7** was converted to the pyrido[2,3-*d*]pyrimidine **8**[10] in 75% yield (Chart 2). Reaction of **1** with (cyanomethylene)triphenylphosphorane in refluxing acetonitrile directly gave a cyclized product, pyrido[2,3-*d*]pyrimidine **9**,[11] in 73% yield. The Wittig reaction of the corresponding aldehyde **2** at room temperature resulted in recovery of the starting material.

Table 1. Reaction of 6-Amino-1,3-dimethyl-5-thioformyluracil **1** and 6-Amino-5-formyl-1,3-dimethyluracil **2** with Amino Compounds



1: X = S
2: X = O

3a-d

Starting compd.	Amino compd.	Reaction conditions	Product	R	Yield (%)
1	$PhNHNH_2$	r.t., inst.[a]	**3a**	NHPh	95
1	NH_2OH	r.t., inst.[a]	**3b**	OH	96
1	$MeNH_2$	r.t., 15 min	**3c**	Me	83
1	$PhNH_2$	r.t., 70 min	**3d**	Ph	89
2	$PhNHNH_2$	r.t., inst.[a]	**3a**	NHPh	48
2	NH_2OH	r.t., 20 h	**3b**	OH	53
2	$MeNH_2$	r.t., 11 h	**3c**	Me	89
2	$PhNH_2$	r.t., 24 h	**3d**	Ph	0
2	$PhNH_2$	Reflux, 24 h	**3d**	Ph	50

a) Instantaneous.

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* To whom correspondence should be addressed.

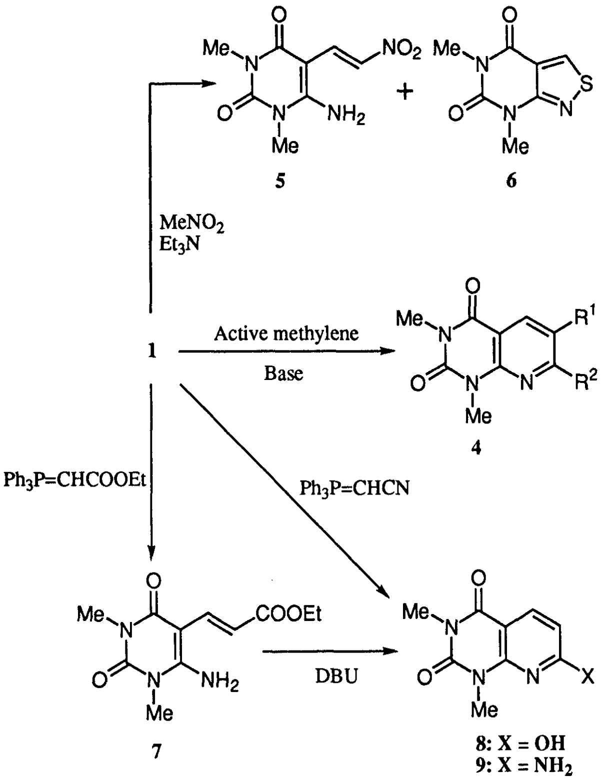

Chart 2

Table 2. Reaction of 6-Amino-1,3-dimethyl-5-thioformyluracil **1** with Active Methylene Compounds

Active methylene	Base	Reaction time (h)	Product	R^1	R^2	Yield (%)
$CH_2(CN)_2$	Et_3N	1	**4a**	CN	NH_2	97
$CH_2(CN)COOEt$	Et_3N	24	**4b**	COOEt	NH_2	59
$CH_2(COOEt)_2$	NaOEt	0.5	**4c**	COOEt	OH	91

Table 3. Reaction of 6-Amino-1,3-dimethyl-5-thioformyluracil **1** and 6-Amino-5-formyl-1,3-dimethyluracil **2** with Wittig Reagents

Starting compd.	Wittig reagent	Reaction temp.	Reaction time (h)	Product	Yield (%)
1	$Ph_3P=CHCOOEt$	r.t.	24	**7**	79
2	$Ph_3P=CHCOOEt$	Reflux	12	**7**	20
1	$Ph_3P=CHCN$	Reflux	4	**9**	73
2	$Ph_3P=CHCN$	Reflux	12	**9**	39

On heating the reaction mixture to reflux, **7** and **9** were formed in low yields (see Table 3).

In summary, the thioaldehyde **1** possess much higher reactivities toward nucleophiles than the corresponding aldehyde **3**. The reactions offer a convenient access to pyrido[2,3-*d*]pyrimidines **4**, **8**, and **9**.[8,10–12]

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. UV spectra were measured in EtOH with Shimadzu UV-260 spectrophotometer. ^{1}H-NMR spectra were determined with a JEOL JNM FX-100 and/or a Hitachi-Perkin Elmer R-20B with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard. Mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV.

6-Amino-1,3-dimethyluracil-5-carboxyaldehyde Phenylhydrazone (3a) (a) A mixture of **1**[5m] (0.40 g, 2 mmol) and phenylhydrazine (0.49 g, 6 mmol) in EtOH (25 ml) was stirred at room temperature. The precipitate, which formed instantaneously, was collected on a suction filter to afford **3a** (0.65 g, 95%). An analytical sample was obtained by recrystallization from AcOH, mp 282—283 °C. MS *m/z*:273 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 350 (4.27). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (s, 3H, NCH_3), 3.39 (s, 3H, NCH_3), 6.95 (m, 5H, Ph), 8.31 (s, 1H, CH=N), 8.69 (br, 2H, NH_2), 9.98 (br s, 1H, NH). *Anal.* Calcd for $C_{13}H_{15}N_5O_2$: C, 57.13; H, 5.53; N, 25.63. Found: C, 56.86; H, 5.53; N, 25.41.

(b) A mixture of **2**[7] (0.37 g, 2 mmol), and phenylhydrazine (0.65 g, 6 mmol) in EtOH (20 ml) was stirred for 24 h. The resulting precipitate was collected on a suction filter to afford **3a** (0.26 g, 48%). This product was identical with the sample obtained by procedure (a).

6-Amino-1,3-dimethyluracil-5-carboxyaldehyde Oxime (3b) (a) A mixture of **1** (0.40 g, 2 mmol), hydroxylamine hydrochloride (0.49 g, 7 mmol) and triethylamine (0.61 g, 6 mmol) in EtOH (20 ml) was stirred at room temperature. The resulting precipitate was collected on a suction filter to afford the oxime **3b** (0.38 g, 96%). An analytical sample was obtained by recrystallization from water, mp 258—260 °C. MS *m/z*: 198 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 268. ^{1}H-NMR (DMSO-d_6) δ: 3.13 (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 7.90—8.57 (br, 3H, CH=N and NH_2), 10.38 (br, 1H, OH). *Anal.* Calcd for $C_{13}H_{15}N_5O_2$: C, 42.42; H, 5.09; N, 28.27. Found: C, 56.86; H, 5.53; N, 25.41.

(b) A mixture of **2** (0.37 g, 2 mmol) hydroxylamine hydrochloride (0.49 g, 7 mmol) and triethylamine (0.61 g, 6 mmol) in EtOH (20 ml) was stirred at room temperature for 24 h. The resulting precipitate was collected on a suction filter to afford **3b** (0.21 g, 53%). This product was identical with the sample obtained by procedure (a).

6-Amino-1,3-dimethyl-5-[(methylimino)methyl]uracil (3c) A mixture of **1** (0.40 g, 2 mmol) and methylamine (30% MeOH solution, 1.04 g, 10 mmol) in EtOH (10 ml) was stirred at room temperature for 15 min. The solvents were evaporated off under reduced pressure and the residue was triturated with ether (20 ml) to afford **3c** (0.35 g, 83%). An analytical sample was obtained by recrystallization from MeOH, mp 232—233 °C. MS *m/z*: 196 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 287 (4.13), 260 (4.13). ^{1}H-NMR (DMSO-d_6) δ: 3.15 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 7.90 (br, 1H, NH), 8.42 (br d, 1H, $J=2$ Hz, CH=N), 11.08 (br, 1H, NH). *Anal.* Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.17; N, 28.56. Found: C, 48.97; H, 6.20; N, 28.48.

(b) A mixture of **2** (0.37 g, 2 mmol) and methylamine (30% MeOH solution, 1.04 g, 10 mmol) in EtOH (10 ml) was stirred at room temperature for 11 h. The solvents were evaporated off under reduced pressure and the residue was triturated with ether (20 ml) to afford **3c** (0.35 g, 89%). This product was identical with the sample obtained by procedure (a).

6-Amino-1,3-dimethyl-5-[(phenylimino)methyl]uracil (3d) (a) A mixture of **1** (0.40 g, 2 mmol) and aniline (0.56 g, 6 mmol) in EtOH (10 ml) was stirred at room temperature for 70 min. The resulting precipitate was collected on a suction filter to afford **3d** (0.46 g, 89%), mp 259—260 °C. MS *m/z*: 258 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 324 (4.32), 266 (4.26). ^{1}H-NMR (DMSO-d_6) δ: 3.22 (s, 3H, NCH_3), 3.39 (s, 3H, NCH_3), 7.27 (m, 5H, Ph), 8.34 (br, 1H, NH), 8.76 (s, 1H, CH=N), 11.11 (br, 1H, NH). *Anal.* Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70. Found: C, 60.64; H, 5.55; N, 21.67.

(b) A mixture of **2** (0.37 g, 2 mmol) and aniline (0.56 g, 6 mmol) in EtOH (10 ml) was refluxed for 50 h. The resulting precipitate was collected on a suction filter to afford **3d** (0.26 g, 50%). This product was identical with the sample obtained by procedure (a).

7-Amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a) A mixture of **1** (0.40 g, 2 mmol), malononitrile (0.40 g, 6 mmol) and triethylamine (3 drops) in EtOH (20 ml) was stirred at room temperature for 1 h. The resulting precipitate was collected on a suction filter to afford **4a** (0.45 g, 97%). Product **4a** recrystallized from AcOH was identical with an authentic sample.[8b]

7-Amino-6-ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (4b) A mixture of **1** (0.40 g, 2 mmol), ethyl cyanoacetate (0.68 g, 6 mmol) and triethylamine (3 drops) in EtOH (20 ml) was stirred at room temperature for 24 h. The resulting precipitate was collected on a suction filter to afford **4b** (0.33 g, 59%). Product **4b** recrystallized from EtOH was identical with an authentic sample.[8b]

6-Ethoxycarbonyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4c) A mixture of **1** (0.40 g, 2 mmol) and diethyl malonate (1.06 g, 6.6 mmol) in ethanolic sodium ethoxide [prepared from Na

(0.14 g, 6 mmol) in absolute EtOH (20 ml)] was stirred under an argon atmosphere at room temperature for 0.5 h. The resulting precipitate was collected on a suction filter and washed with water (20 ml × 2) to afford **4c** (0.51 g, 91%). An analytical sample was obtained by recrystallization from AcOH, mp 172—174 °C (lit.[8c)] mp 166—170 °C). MS *m*/*z*: 279 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 317 (4.23), 275 (3.99). The ^{1}H-NMR data for **4c** were identical with the reported values.[8c)]

Reaction of the 5-Thioformyluracil 1 with Nitromethane A mixture of **1** (0.40 g, 2 mmol) and triethylamine (3 drops) in nitromethane (10 ml) was refluxed for 18 h. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by elution from a silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to yield 0.10 g of 1,3-dimethylisothiazolo[3,4-*d*]pyrimidine-2,4-dione (**6**) (25%) and 0.12 g of (*E*)-6-amino-1,3-dimethyl-5-(2-nitrovinyl)uracil (**5**) (27%) in this order. Compound **6** thus obtained was identical with an authentic sample.[5m)] An analytical sample of **5** was obtained by recrystallization from MeOH, mp 228—230 °C. MS *m*/*z*: 226 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 393 (4.30), 274 (3.96), 234 (3.92). ^{1}H-NMR (DMSO-d_6) δ: 3.16 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 8.13 (d, 1H, $J = 21.0$ Hz, $C\underline{H}=CHNO_2$), 8.25 (br, 2H, NH_2), 8.49 (d, 1H, $J = 21.0$ Hz, $NO_2C\underline{H}=CH$). *Anal* Calcd for $C_8H_{10}N_4O_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.52; H, 4.51; N, 24.71.

Ethyl (*E*)-3-(6-Amino-1,3-dimethyluracil-5-yl)acrylate (7) (a) A mixture of **1** (0.30 g, 1.5 mmol) and (carbethoxymethylene)triphenylphosphorane (0.78 g, 2.25 mmol) in dry acetonitrile (10 ml) was stirred under an argon atmosphere at room temperature for 24 h. The resulting precipitate was collected on a suction filter to afford **7** (0.30 g, 79%), and the filtrate was concentrated under reduced pressure. The residue was purified by elution from a silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to yield 0.36 g of triphenylphosphine sulfide (69%) which was identical with a commercial sample (Aldrich Chemical Company, Inc.). Compound **7** thus obtained was recrystallized from EtOH, mp 227—229 °C (lit.[10a)] mp 237—238 °C) MS *m*/*z*: 253 (M^+). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 325 (4.30), 276 (4.03). The ^{1}H-NMR data for **7** were identical with the reported values.[10a)]

(b) A mixture of **2** (0.18 g, 1 mmol) and (carbethoxymethylene)-triphenylphosphorane (0.52 g, 1.5 mmol) in dry acetonitrile (10 ml) was refluxed under an argon atmosphere for 12 h. The resulting precipitate was collected on a suction filter to afford **7** (0.05 g, 20%). This product was identical with the sample obtained by procedure (a). The filtrate was concentrated under reduced pressure and the residue was purified by elution from a silica gel column with 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to recover 0.17 g of **2** (77%).

1,3-Dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (8) A mixture of **7** (127 mg, 0.5 mmol) and DBU (15 drops) in dry acetonitrile (10 ml) was refluxed for 24 h. The solvents was evaporated off under reduced pressure, and the residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was washed with dilute $KHSO_4$ solution (20 ml) and brine (20 ml), dried over $MgSO_4$ and evaporated to yield 77 mg of the pyrido[2,3-*d*]pyrimidine **8** (75%). This product was identical with an authentic sample.[10c)]

7-Amino-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (9) (a) A mixture of **1** (0.20 g, 1 mmol) and (cyanomethylene)triphenylphosphorane (0.45 g, 1 mmol) in dry acetonitrile (10 ml) was refluxed under an argon atmosphere for 4 h. The resulting precipitate was collected on a suction filter to afford **9** (0.15 g, 73%). An analytical sample was recrystallized from EtOH, mp 290—295 °C (sublimation) (lit.[11)] mp 309 °C). MS *m*/*z*: 206 (M^+). The UV and ^{1}H-NMR data for **9** were identical with the reported values.[11)]

(b) A mixture of **2** (0.18 g, 1 mmol) and (carbethoxymethylene)-triphenylphosphorane (0.45 g, 1.5 mmol) in dry acetonitrile (10 ml) was refluxed under an argon atmosphere for 12 h. The resulting precipitate was collected on a suction filter to afford **9** (0.08 g, 39%). This product was identical with the sample obtained by procedure (a). The filtrate was concentrated under reduced pressure and the residue was purified by elution from a silica gel column with a 100 : 1 (v/v) mixture of $CHCl_3$ and MeOH to recover 0.06 g of **2** (33%).

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6) The reaction of (2,4,6-tri-*tert*-butyl)thiobenzaldehyde, which is stabilized by steric protection with aniline, did not proceed even under reflux in xylene.[2g)]

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9) Although the formation of **4c** by condensation of **2** with diethyl malonate in the presence of piperidine as a base (refluxed in EtOH for 24h, 42% yield) was reported by Broom *et al.*,[8c)] we could not obtain the pyrido[2,3-*d*]pyrimidine **4c** under our reaction conditions.

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