(m, 4 H, CH_2CH_2), 1.35 (d, J = 7 Hz, 3 H, CH_3); IR ($CHCl_3$, cm^{-1}) 3200–2800 (br s), 1710 (s), 1650 (w), 1600 (w), 1490 (m), 1460 (m), 1310 (m), 990 (s). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.25; H, 7.27.

The acid was also obtained by alkylation of the ester **11** with MeI at −35 °C according to the general procedure followed by saponification of the resulting ester in a mixture of 20 g of KOH in ethanol–water (1:1, v/v).

Acknowledgment. We thank Dr. G. van Koten for stimulating discussions. This work was carried out under the auspices of the Netherlands Foundation for Chemical Research (S.O.N.) with financial support from the Netherlands Organization for Advancement of Pure Research (Z.W.O.).

Registry No. **1**, 625-38-7; **1** (α-methylated), 53774-20-2; **1** (γ-methylated), 5204-64-8; **2**, 1617-32-9; **2** (α,α-dimethylated), 16642-52-7; **3**, 4219-24-3; **3** (α-methylated), 73513-50-5; **3** (α,α-dimethylated), 94041-92-6; **4**, 2243-53-0; **5**, 55131-28-7; **5** (α-methylated), 94041-93-7; **5** (α,α-dimethylated), 55078-29-0; **6**, 54154-71-1; **6** (α-methylated), 41791-34-8; **6** (α,α-dimethylated), 94041-94-8; **7**, 57932-05-5; **7** (α-methylated), 24040-29-7; **7** (γ-methylated), 69381-20-0; **8**, 1617-18-1; **8** (α-methylated), 1647-12-7; **9**, 818-58-6; **9** (α-methylated), 2258-55-1; **10**, 34541-74-7; **11**, 41791-31-5; **11** (α-methylated), 24040-31-1; **11** (α,α-dimethylated), 94041-95-9; **12**, 24040-30-0; **12** (α-methylated), 24040-28-6; **13**, 37674-63-8; **14**, 94041-87-9; **15**, 94041-88-0; **16**, 79164-23-1; **17**, 4405-27-0; $Me_2N^+{=}CH_2{\cdot}I$, 33797-51-2; MeI, 74-88-4; 2-cyclopentylidenecyclopentanone, 825-25-2; 2-(2-methylcyclopentylidene)cyclopentanone, 94041-89-1; crotyl chloride, 591-97-9; cinnamyl bromide, 4392-24-9; 2-(1-cyclopentenyl)-2-methylcyclopentanone, 43011-75-2; 2-(1-cyclopentenyl)-2-crotylcyclopentanone, 94041-90-4; 2-(1-cyclopentenyl)-2-cinnamylcyclopentanone, 94041-91-5; ethyl crotonate, 10544-63-5; propanal, 123-38-6; malonic acid, 141-82-2; ethyl pent-3-enoate, 1617-05-6.

Pyrimido[4,5-*c*]pyridazines. 6. Pyrimido[4,5-*c*]pyridazines and 1,2,4-Triazines from Reactions between 6-Hydrazinopyrimidin-4(3*H*)-ones and Vicinal Dicarbonyl Reagents

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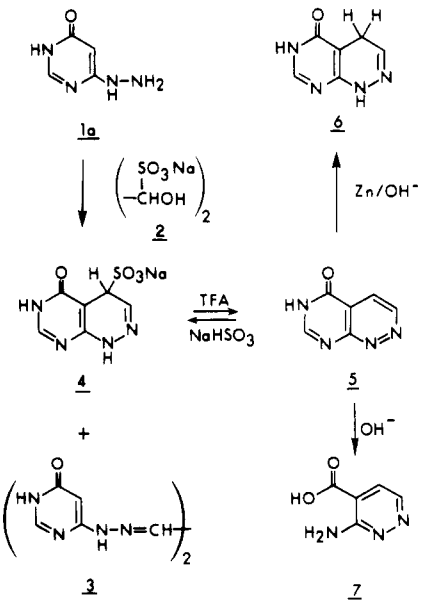
Reactions between 6-hydrazinopyrimidin-4(3*H*)-ones and selected vicinal dicarbonyl reagents have produced novel hydrazonopyrimidines, pyrimidopyridazines, and 1,2,4-triazin-5(2*H*)-ones. Criteria for the successful cyclizations, unexpected physical/chemical properties of the compounds, and a peculiar sodium salt are described.

Reactions of hydrazinopyrimidines with various vicinally functionalized reagents have been unpredictable. Depending upon the properties of both reactants, different products have resulted, including stable hydrazones, bis(hydrazones), pyrimido[4,5-*c*]pyridazines, pyrimido[4,5-*c*]-1,2-diazepines, and pyrrolo[2,3-*d*]pyrimidines.[1-5] Investigation of another hydrazinopyrimidine series has provided more unusual and sometimes unexpected chemistry. Selected reactions of 6-hydrazinopyrimidin-4(3*H*)-ones and vicinal carbonyl reagents are described in this paper. Properties of the products and some of their derivatives are also discussed.

Discussion

6-Hydrazinopyrimidinone **1a** and sodium bisulfite addition compound of glyoxal (**2**) reacted to give a mixture of bis(hydrazone) (**3**) and a pyrimido[4,5-*c*]pyridazine (Scheme I). The cyclization product was isolated as the bisulfite adduct **4**; however, bisulfite addition (determined by NMR to be 1,4) was readily reversible. Treatment of **4** with CF_3COOH liberated the heteroaromatic species **5**, which reverted to **4** in aqueous sodium bisulfite. As expected,[5] compound **5** was reduced to stable 1,4-dihydro derivative **6** with Zn/OH^-, but **5** is labile to aqueous base or boiling water alone. Treatment of **5** with refluxing 1 N NaOH for 1 h provided pyridazinecarboxylic acid **7**[6] in high yield (94%). Similar instability affects other compounds described in this paper.

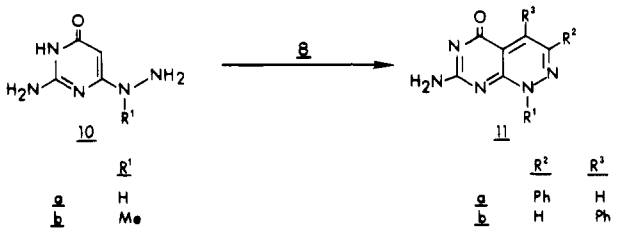
Scheme I



(1) Pfleiderer, W.; Ferch, H. *Liebigs Ann. Chem.* **1958**, *615*, 48.
(2) Morrison, R. W., Jr.; Mallory, W. R.; Styles, V. L. *J. Org. Chem.* **1978**, *43*, 4844.
(3) Mallory, W. R.; Morrison, R. W., Jr.; Styles, V. L. *J. Org. Chem.* **1982**, *47*, 667.
(4) Styles, V. L.; Morrison, R. W., Jr. *J. Org. Chem.* **1982**, *47*, 585.
(5) Morrison, R. W., Jr.; Styles, V. L. *J. Org. Chem.* **1982**, *47*, 674.
(6) Nakagome, T.; Castle, R. N.; Murakami, H. *J. Heterocycl. Chem.* **1968**, *5*, 523.

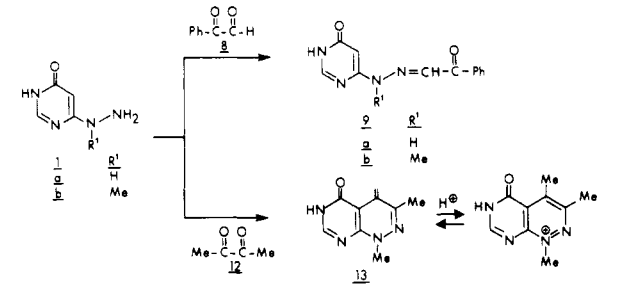
0022-3263/85/1950-0346$01.50/0

Cyclization was not observed from the reactions of either **1a** or **1b** and phenylglyoxal (**8**); only stable hydrazones **9** were isolated. In contrast, as previously reported,[5] the isocytosine analogues (**10**) of **1a,b** and **8** undergo cyclization to give pyrimidopyridazines **11**. Because of the 2-amino substituent's electron-releasing influence, the isocytosine C-5 position was reactive enough to effect cyclization.

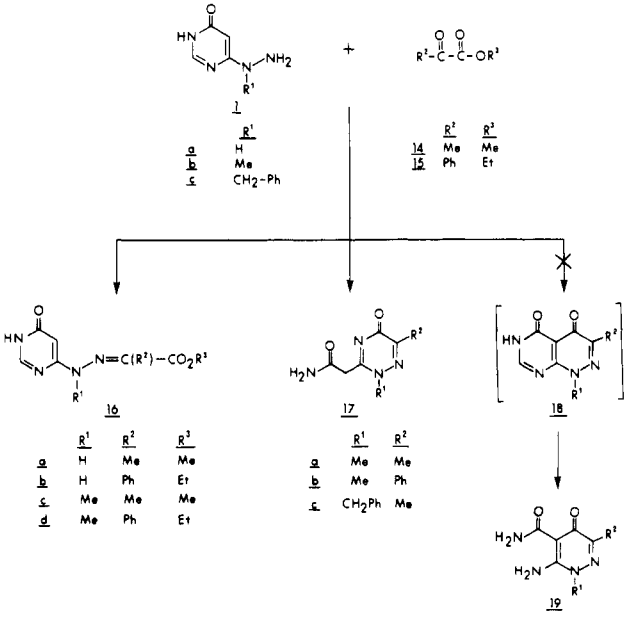


	R^1		R^2	R^3
a	H	**a**	Ph	H
b	Me	**b**	H	Ph

Hydrazinopyrimidinone **1b** and diacetyl **12** did react slowly to give 1,4-dihydropyrimidopyridazine **13**. The chance for cyclization was better because the cyclizing agent was a more reactive ketone (compared to the phenyl ketone moiety in **8**). Compound **13** has two p*K*a values (9.8 and 5.3); based on NMR, protonation occurs on the exocyclic carbon at C-4.



As predicted,[5] the reactions of **1a** with α-keto esters **14** and **15** yielded stable hydrazones **16a,b** instead of pyrimidopyridazines. Furthermore, no pyrimidopyridazines **18** resulted from the reactions of **1b,c** and the α-keto esters.

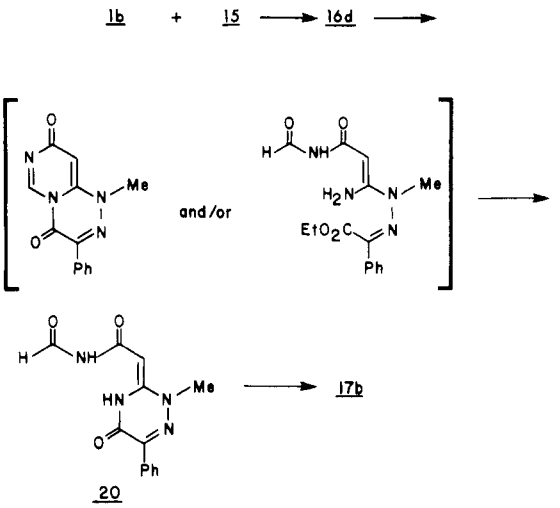


	R^1	R^2	R^3
a	H	Me	Me
b	H	Ph	Et
c	Me	Me	Me
d	Me	Ph	Et

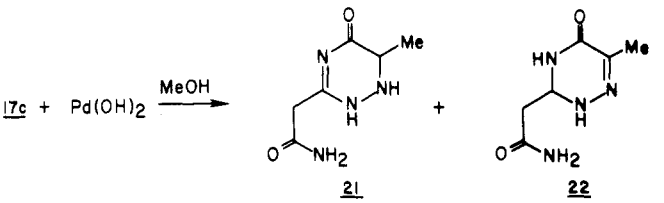
	R^1	R^2
a	Me	Me
b	Me	Ph
c	CH_2Ph	Me

Hydrazones **16c,d** formed initially, but longer reaction times afforded 1,2,4-triazines **17** in good yield. Isomeric pyridazines **19** were eliminated by NMR spectroscopy (which indicated a methylene signal). Reaction between ethyl phenylglyoxylate **15** and **1b** also provided intermediate **20**, which further defines the reaction pathway to triazine **17b**, but the cyclization–pyrimidine degradation sequence was undetermined (Scheme II). Triazine formation is favored because, without appropriate substitution (i.e., electron donation at C-2), the pyrimidine ring lacks sufficient activation to cyclize at C-5 and is vulnerable to hydrolytic attack.

Scheme II



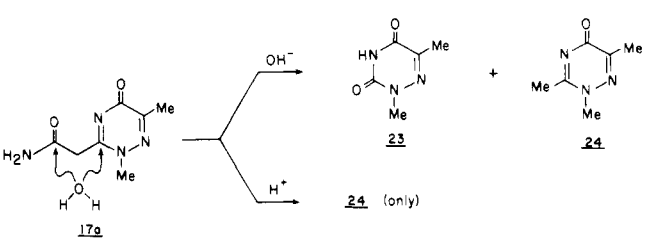
Synthesis of 1,2,4-triazines by this new ring transformation procedure is limited by the need for alkylation of the pyrimidine precursor's hydrazine moiety; however, an unsubstituted derivative was prepared indirectly from *N*-benzyl analogue **17c**. Pearlman's catalyst [$Pd(OH)_2$ on carbon] was adequate for the debenzylation, but hydrogenolysis was accompanied by partial reduction of the triazine ring. A 9:1 mixture of isomers **21** and **22** resulted when the solvent was methanol.



Triazine **17a**, itself a hydrolytic degradation product, can be degraded by either acid- or base-catalyzed hydrolysis (Scheme III). When treated with 1.0 N NaOH, **17a** provided a mixture of azauracil **23** and 3-methyltriazine **24**, but acidolysis selectively yielded **24**. Hydrolytic attack at the amide moiety promotes formation of compound **24**, whereas dione formation (**23**) requires initial attack at C-3 of the triazine ring.

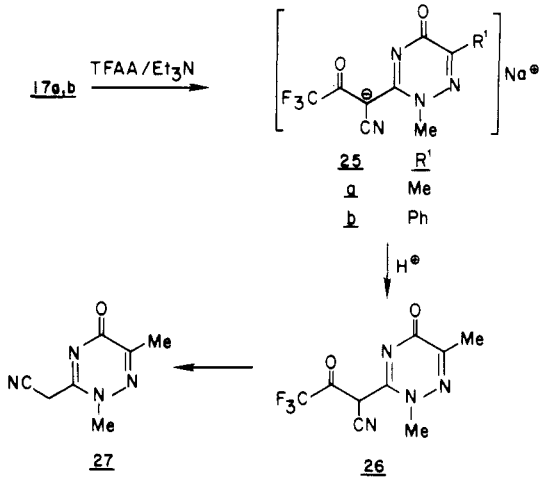
In another study, conversion of the amide moiety to a nitrile by an adaptation of Campagna and co-workers' method[7] did not proceed straightforwardly. When treated with trifluoroacetic anhydride in tetrahydrofuran, triazines **17a,b** were dehydrated and trifluoroacetylated at the methylene carbon. The products were isolated as sodium salts **25** after extraction from an aqueous solution with

Scheme III



(7) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

chloroform (or methylene chloride) and subsequent chromatography on silica gel with ethyl acetate. A remarkable feature of the sodium derivative's (**25a**[8]) electron impact mass spectrum was the presence of a molecular ion at m/e 282, which was peak matched as $C_9H_6N_4O_2F_3Na$. Free acid **26** was generated from the salt by neutralization with aqueous HCl, but prolonged mild acid treatment effected cleavage of the trifluoroacetyl group to give cyanomethyl derivative **27**.



Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus. NMR (Fourier Transform) spectra were obtained on Varian XL-100 and CFT- 80 spectrometers with tetramethylsilane as the standard. IR spectra were recorded on a Perkin-Elmer grating spectrophotometer. Quantitative UV spectra were recorded on a Cary 118 spectrophotometer. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF double-focusing mass spectrometer at 70 eV, and probe temperatures were noted. Field-desorption data were determined with a Varian MAT 731 spectrometer. The TLC data were determined with Whatman MK6F silica gel plates. Microanalyses were performed at Burroughs Wellcome Co. or at Atlantic Microlab, Inc., Atlanta, and were acceptable (±0.4%). All C,H,N analyses not reported here can be found, along with other physical data, in the supplementary material section.

6-(1-Benzylhydrazino)-4(3*H*)-pyrimidinone (1c). To a mixture of 4-chloropyrimidin-6(1*H*)-one[9] (18.0 g, 0.138 mol) and benzylhydrazine dihydrochloride[10] (40.4 g, 0.207 mol) in 95% EtOH (200 mL) at room temperature was added triethylamine[11] (55.9 g, 0.55 mol). The mixture was heated to reflux during a 0.25-h period, giving a complete, yellow solution. Reflux was continued for 1.75 h during which time a thick, white precipitate formed. The mixture was allowed to cool to ambient temperature before filtration. Triethylamine hydrochloride that coprecipitated with the product was removed by washing with H_2O. The white solid was dried under vacuum (70 °C): yield 21.6 g (72%) of white powder; mp 215–218 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 4.50 (br s, 2 H), 4.85 (s, 2 H), 5.55 (s, 1 H), 7.23 (s, 5 H), 7.86 (s, 1 H), 11.50 (br s, 1 H); UV (MeOH) λ_{max} 227 nm (ε 23 100), 267.5 (12 600); TLC (*n*-BuOH:HOAc:H_2O/3:1:1), R_f 0.55 (stains yellow with ninhydrin). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 60.95; H, 5.65; N, 25.82.

Compound **1b** was prepared similarly.

6-(1-Methylhydrazino)pyrimidin-4(3*H*)-one (1b). Molar ratio of methylhydrazine (**14**):4-chloropyrimido-6-(1*H*)-one:triethylamine, 1:2.5:1; 1 h reflux: yield 94%; mp 235.5–236.5 °C dec. Anal. ($C_5H_8N_4O$).

1,2-Bis[(4-oxo-3,4-dihydro-6-pyrimidinyl)hydrazono]-ethane (3) and Pyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5). Compound **1a**[12] (12.6 g, 0.10 mol) was added at once to a stirred, refluxing solution of glyoxal sodium bisulfite addition compound monohydrate **2**[10] (56.8 g, 0.20 mol) in H_2O (1.0 L). Orange solid precipitated immediately. Reflux was continued for 1.25 h before the mixture was filtered while hot. The orange, amorphous solid was washed with H_2O (2 × 15 mL) and dried under vacuum (70 °C): yield 6.0 g (44%, increased to 59% when the molar ratio of **1a** to **2** was 1:1) of **3**; mp >300 °C; ^{1}H NMR (CF_3COOH) δ 6.58 (s, 2 H), 8.00 (s, 2 H), 9.08 (s, 2 H); UV (0.1 N NaOH) λ_{max} 242 nm sh (ε 13 700), 270 sh (8900), 352 (47 900), 400 sh (5800); mass spectrum (70 eV, 365 °C), m/z 274 (M, 3%), 164 (22), 137 (18), 28 (100). Anal. Calcd for $C_{10}H_{10}N_8O_2$: C, 43.80; H, 3.68; N, 40.86. Found: C, 43.55; H, 3.67; N, 41.05.

The yellow filtrate was treated with sodium bisulfite (20.8 g, 0.20 mol), concentrated at reduced pressure to 400 mL, and allowed to stand for 18 h at ambient temperature. The off-white crystals that separated were collected by filtration, washed with H_2O (2 × 5 mL), and dried under vacuum (70 °C): yield 5.2 g of the bisulfite adduct **4** (identified by NMR and UV). This solid was warmed with CF_3COOH (50 mL) on a steam bath until complete solution occurred (~10 min). The orange solution was allowed to cool to ambient temperature before being concentrated under vacuum (35 °C bath) to an orange oil. The oil was treated with H_2O (25 mL) to provide pale tan crystals. The product (**5**) was collected by filtration and washed (H_2O): yield 2.38 g (16%); mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.25 (d, J = 5 Hz, 1 H), 8.43 (s, 1 H), 9.49 (d, J = 5 Hz, 1 H), 12.77 (br s, 1 H); ^{1}H NMR (CF_3COOH) δ 8.98 (s, 1 H), 9.26 (d, J = 5 Hz, 1 H), 9.72 (d, J = 5 Hz, 1 H); UV (95% EtOH) λ_{max} 262 nm (ε 5800), 311 (4500); mass spectrum (70 eV, 150 °C), m/z 148 (M, 100%), 120 (9), 93 (28), 65 (99); TLC (EtOAc:MeOH/4:1), R_f 0.28. Anal. Calcd for $C_6H_4N_4O$: C, 48.65; H, 2.72; N, 37.83. Found: C, 48.59; H, 2.76; N, 37.87.

Sodium 5-Oxo-1,4,5,6-tetrahydropyrimido[4,5-*c*]-pyridazine-4-sulfonate Hydrate (4). To a solution of sodium bisulfite (2.07 g) in H_2O (150 mL) was added **5** (1.18 g, 7.97 mmol). The mixture was warmed until complete solution occurred. The hot solution was filtered, concentrated to 20 mL, and allowed to cool to ambient temperature. The colorless crystals that separated were collected and dried under vacuum (25 °C): yield 2.08 g (97%); mp >300 °C; NMR (Me_2SO-d_6) δ 4.41 (d, J = 4 Hz, 1 H), 6.68 (d, J = 4 Hz, 1 H), 7.87 (s, 1 H), 10.36 (s, 1 H), 11.81 (br s, 1 H); uv (pH 5.2 buffer) λ_{max} 245 nm (ε 10 400), 305 (3100). Anal. Calcd for $C_6H_5N_4NaO_4S$·H_2O: C, 26.67; H, 2.61; N, 20.74; Na, 8.51; S, 11.87. Found: C, 26.63; H, 2.61; N, 20.70; Na, 8.48; S, 11.81.

1,4-Dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (6). Under nitrogen, a mixture of **5** (1.70 g, 11.5 mmol) and purified zinc dust[5] (5.0 g) in 2 N NaOH (75 mL) was stirred and heated to reflux during a 10-min period. Reflux was continued for 1 h before insoluble inorganic solids were removed by filtration. While hot, the filtrate was quickly adjusted to pH 6.2 with glacial HOAc to precipitate the product as a white solid. The mixture was allowed to cool to room temperature under nitrogen before the product was collected by filtration, washed with H_2O, and dried under vacuum (70 °C): yield 1.56 g (90%); mp 285 °C dec; NMR (Me_2SO-d_6) δ 3.06 (d, J = 3 Hz, 2 H), 6.68 (t, J = 3 Hz, 1 H), 7.80 (s, 1 H), 10.03 (br s, 1 H), 11.91 (br s, 1 H); UV (pH 5.16 buffer) λ_{max} 239 nm (ε 10 400), 307 (3200); TLC (EtOAc:MeOH/7:3), R_f 0.47. Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.93; H, 4.05; N, 37.30.

3-Amino-4-pyridazinecarboxylic Acid (7).[6] A solution of **5** (2.18 g, 0.0147 mol) in 1.0 N NaOH (50 mL) was heated at reflux for 1.5 h, adjusted to pH 2.0 with concentrated HCl, and allowed to stand at room temperature for 1 h. The off-white precipitate was collected by filtration, washed with H_2O (3 × 3 mL), and dried under vacuum (70 °C): yield 1.93 g (94%); mp 261–263 °C [lit. mp 261–262 °C dec]. Anal. ($C_5H_5N_3O_2$).

Compound **5** was also degraded slowly in H_2O alone at reflux for 48 h.

1,4-Dihydro-1,3-dimethyl-4-methylenepyrimido[4,5-*c*]-pyridazin-5(6*H*)-one (13). To a mixture of **1b** (0.70 g, 5.0 mmol) and MeOH (20 mL) at reflux was added 2,3-butanedione (0.69 g, 8.0 mmol). Reflux was continued for 48 h. The resulting

(8) Prof. A. McPhail at Duke University carried out an X-ray crystallographic analysis of **26a**, which he plans to report in a separate paper.
(9) Brown, J. D.; Harper, J. S. *J. Chem. Soc.* **1961**, 1298.
(10) Aldrich Chemical Company.
(11) Eastman Kodak Company.
(12) Brown, D. J.; Lynn, R. K. *Aust. J. Chem.* **1974**, *27*, 1781.

precipitate was collected by suction filtration and subsequently recrystallized from MeOH: yield 0.24 g (25%); mp 217–219 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.95 (s, 3 H), 3.45 (s, 3 H), 4.74 (d, J = 1.5 Hz, 1 H), 6.16 (d, J = 1.5 Hz, 1 H), 7.98 (s, 1 H), 12.12 (br s, 1 H); ^{1}H NMR (CF_3COOH) δ 2.93 (s, 3 H), 3.23 (s, 3H), 4.74 (s, 3 H), 8.68 (s, 1 H); UV (MeOH) λ_{max} 250 nm (ε 12 700), 263.5 (13 200), 318 (6800), 330.5 (6300), 370 (2000); mass spectrum (70 eV), m/z 190 (M, 100%), 162 (19), 148 (79), 121 (17), 120 (21), 93 (18); mass spectrum (field-desorption), 190 (M); TLC (ethyl acetate), R_f 0.7; pKa 9.77 and pKa 5.32. Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.75; H, 5.36; N, 29.40.

Ethyl 2-[(1,6-Dihydro-6-oxo-4-pyrimidinyl)hydrazono]-2-phenylacetate (16b). A mixture of **1a**[12] (1.26 g, 0.01 mol) and **15**[11] (2.67 g, 0.015 mol) in 95% EtOH (40 mL) was refluxed for 0.5 h. The resulting pale yellow solution was filtered while hot and allowed to stand at room temperature for 2 h. The colorless needles that had separated were collected, washed with 95% EtOH, and dried under vacuum (50 °C): yield 2.25 g (79%); mp 201–203 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.30 (t, J = 7.1 Hz, 3 H), 4.39 (q, J = 7.1 Hz, 2 H), 5.93 (s, 1 H), 7.36–7.49 (m, 3 H), 7.59–7.72 (m, 2 H), 8.08 (d, J = 0.5 Hz, 1 H), 11.32 (br s, 1 H), 11.78 (br, 1 H); UV (MeOH) λ_{max} 232 (ε 19 800), 273 (9200), 342 (19 700). Anal. Calcd for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.64; H, 4.93; N, 19.54.

A solution of **16b** (200 mg) in 95% EtOH (100 mL) was heated at reflux for 72 h with no apparent change.

Similarly prepared were **9a,b**, **16a**, and **16c**. The starting hydrazinopyrimidine derivative, starting vicinal dicarbonyl reagent, solvent (mL/mmol of pyrimidine), and reaction time are given in brackets, followed by the yield and melting point.

6-[2-(Benzoylmethylene)hydrazino]-4(3*H*)pyrimidinone (9a) [**1a**,[12] phenylglyoxal (8),[10] H_2O (15), 1 h]: 88%; mp 281–284 °C dec. Anal. ($C_{12}H_{10}N_4O_2$). Compound **9a** did not cyclize in either glacial HOAc (19 h) or MeOH (2 days) at reflux.

6-[2-(Benzoylmethylene)-1-methylhydrazino]-4(3*H*)-pyrimidinone (9b) [**1a**, phenylglyoxal (8),[10] H_2O (15), 0.5 h]: 77% after recrystallization from MeOH; mp 239.5–241 °C dec. Anal. ($C_{13}H_{12}N_4O_2$: $^2/_5$ MeOH). Compound **9b** was unchanged after 72 h in refluxing MeOH.

Methyl 2-[(1,6-dihydro-6-oxo-4-pyrimidinyl)hydrazono]-propionate (16a) [**1a**,[12] **14**,[10] MeOH (9), 1.0 h]: 52%; mp 223–224 °C dec. Anal. ($C_8H_{10}N_4O_3$). Compound **16a** was unchanged after 66 h in refluxing MeOH.

Methyl 2-[(1,6-dihydro-6-oxo-4-pyrimidinyl)methylhydrazono]propionate (16c) [**1b**, **14**,[10] MeOH (4), 0.5 h]: 67%; mp 159.5–160.5 °C. Anal. ($C_9H_{12}N_4O_3$).

The Reaction of 6-(1-Methylhydrazino)-4(3*H*)-pyrimidinone and Ethyl Phenylglyoxylate in 95% Ethanol. (A) Ethyl 2-[(1,6-Dihydro-6-oxo-4-pyrimidinyl)methylhydrazono]-2-phenylacetate (16d). To a mixture of **1b** (0.70 g, 5.0 mmol) and 95% EtOH (20 mL) at reflux was added **15**[11] (1.34 g, 7.5 mmol, freshly distilled). The resulting solution was heated at reflux for 15 min before filtration while hot (gravity, fritted glass funnel). EtOH (95%, 2 mL) was added to facilitate transfer. The clear, yellow filtrate was allowed to stand at room temperature for 4 h. The bright yellow needles that had separated were collected by suction filtration, washed with 95% EtOH (3 × 1 mL), and dried under vacuum at 25 °C: yield 1.05 g (70%); mp 139.5–141 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.31 (t, J = 7 Hz, 3 H), 3.46 (s, 3 H), 4.43 (q, J = 7 Hz, 2 H), 5.92 (s, 1 H), 7.50 (m, 5 H), 8.07 (s, 1 H), 11.3 (br s, 1 H). Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.82; H, 5.44; N, 18.72.

Increasing the reflux time to 1 h afforded a 78% yield of a 3.1:1.0 mixture of **16d**:**20**.

(B) *N*-Formyl-2-(2,3,4,5-tetrahydro-2-methyl-5-oxo-6-phenyl-1,2,4-triazin-3-ylidine)acetamide (20). When the reflux time was increased to 100 h and the resulting mixture was allowed to stand at ambient temperature for 48 h, an 86% yield of a 4:1 mixture of **20**:**17b** was obtained. After 100 h reflux, the mixture was filtered while hot, and only **20** was obtained (56%): mp 209–211.5 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.57 (s, 3 H), 4.70 (s, 1 H), 7.41–7.53 (m, 3 H), 7.90–7.99 (m, 2 H), 9.01 (d, J = 9.7 Hz, 1 H, collapsed to a singlet with D_2O), 10.65 (br d, J = 9.7 Hz, 1 H), 12.80 (br s, 1 H); TLC (EtOAc:MeOH/4:1), R_f 0.79. Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.37; H, 4.48; N, 20.58.

2-(2,6-Dimethyl-2,5-dihydro-5-oxo-1,2,4-triazin-3-yl)acetamide (17a). To a mixture of **1b** (1.40 g, 0.01 mol) and MeOH (40 mL) was added **14**[10] (1.53 g, 0.015 mol) at room temperature. Under nitrogen, the mixture was refluxed for 65 h. Reaction progress was monitored by UV (MeOH) and TLC (MeOH). A complete, yellow solution was formed at 17 h, and product had begun to crystallize within 42 h. The mixture was allowed to cool to ambient temperature before filtration. The collected solid was washed with MeOH and dried under vacuum (70 °C): yield 1.47 g (81%); mp 226–227 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.13 (s, 3 H), 3.64 (s, 2 H), 3.75 (s, 3 H), 7.25 (br, 1 H), 7.66 (br, 1 H); UV λ_{max} (MeOH) 247 nm (ε 12 900), 262 sh (8700); mass spectrum (130 °C, 70 eV), m/z 182 (M, 49%), 141 (22), 98 (100); accurate masses 182.0804 ($C_7H_{10}N_4O_2$), 141.0540 ($C_5H_7N_3O_2$, M − MeCN); ^{13}C NMR (Me_2SO-d_6) δ 16.6 q (6-Me), 42.0 t (CH_2), 43.2 q (N-Me), 151.4 s (C-6 or C-3), 159.3 s (C-3 or C-6), 162.2 s (C-5, C=O), 167.8 s (exocyclic C=O); TLC (MeOH), R_f 0.65. Anal. Calcd for $C_7H_{10}N_4O_2$: C, 46.14; H, 5.53; N, 30.75. Found: C, 46.13; H, 5.57; N, 30.77.

Triazine **17c** was similarly prepared. The starting hydrazinopyrimidine derivative, starting α-keto ester and reaction time are given in brackets, followed by the yield and melting point.

2-(2-Benzyl-2,5-dihydro-6-methyl-5-oxo-1,2,4-triazin-3-yl)acetamide (17c) [6-(1-Benzylhydrazino)-4(3*H*)-pyrimidinone (**1c**), **14**, 79 h]: 75%; mp 179–181 °C. Anal. $C_{13}H_{14}N_4O_2$.

2-(2,5-Dihydro-2-methyl-5-oxo-6-phenyl-1,2,4-triazin-3-yl)acetamide (17b). A solution of **20** (50 mg, 0.18 mmol) in MeOH (100 mL) was heated at reflux for 25 h, although no further change in UV was detected after 6 h. The pale yellow solution was concentrated under vacuum to a small volume (ca. 2 mL) and allowed to stand for 0.25 h. The pale yellow crystals were collected by filtration, washed with MeOH (0.5 mL), and dried under vacuum (70 °C): yield 33 mg (75%); mp 215–218 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.74 (s,2 H), 3.90 (s, 3 H), 7.34 (br, 1 H), 7.40–7.52 (m, 3 H), 7.73 (br, 1 H), 8.03–8.16 (m, 2 H); UV (MeOH) λ_{max} 260 nm (ε 8400), 296 (12 900); TLC (EtOAc:MeOH/4:1), R_f 0.36. Anal. Calcd for $C_{12}H_{12}N_4O_2$: C, 59.00; H, 4.95; N, 22.94. Found: C, 59.02; H, 4.97; N, 22.94.

2-(1,2,5,6-Tetrahydro-6-methyl-5-oxo-1,2,4-triazin-3-yl)-acetamide (21)[13] **and 2-(2,3,4,5-Tetrahydro-6-methyl-5-oxo-1,2,4-triazin-3-yl)acetamide (22).** A solution of **17c** (0.46 g, 1.86 mmol) in MeOH (45 mL) containing Pearlman's catalyst[10] (0.25 g of 20% palladium hydroxide on carbon) was slowly hydrogenated in a Parr apparatus at an initial hydrogen pressure of 50 psi. After five days, the catalyst was removed by filtration through a Millipore prefilter, and the solvent was evaporated under vacuum to yield a colorless glass (0.26 g), determined by NMR to be a 9:1 isomeric mixture of **21** to **22**. Pure samples of each isomer were obtained as colorless solids by fractional recrystallization from MeOH.

Isomer 21: mp 159–161 °C; NMR (Me_2SO-d_6) δ 1.12 (d, J = 6.5 Hz, 3 H), 3.00 (s, 2 H), 3.25 (dq, J = 2.5 Hz, J = 6.5 Hz, 1 H, simplifies to 8 with D_2O), 6.55 (d, J = 2.5 Hz, 1 H), 6.95 (br, 1 H), 7.31 (br, 1 H), 9.95 (br, 1 H); UV λ_{max} (MeOH) 274 nm (ε 4100); TLC (EtOAc:MeOH/9:1), R_f 0.19. Anal. Calcd for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.34; H, 5.96; N, 32.89.

Isomer 22: mp 204–205 °C dec; NMR (Me_2SO-d_6) δ 1.88 (s, 3 H), 2.47 (d, J = 6.2 Hz, 2 H), 4.73 [m, 1 H, sharpens to t (J = 6.2 Hz) with D_2O], 7.03 (br, 1 H), 7.50 (br, 1 H), 7.76 (br, 1 H), 8.16 (br, 1 H); UV λ_{max} (MeOH) 215 nm (ε 4700), 299 (2200); TLC (EtOAc:MeOH/9:1), R_f 0.2. Anal. Calcd for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.42; H, 5.95; N, 32.87.

Degradation Behavior of 17a. (A) Alkaline Conditions. 2,6-Dimethyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (23)[15] **and 2,3,6-Trimethyl-1,2,4-triazin-5(2*H*)-one (24).**[16] A solution of **17a** (0.64 g, 3.5 mmol) in 1.0 N NaOH (25 mL) was stored in an air-tight flask for 260 h at ambient temperature. The pale yellow

(13) The 1,4,5,6-tetrahydro tautomer cannot be ruled out as a structural possibility on the basis of the physical data in hand.

(14) Similar results were obtained with 5% palladium on carbon except the yield of **22** was increased to 35%. No explanation of the difference is offered.

(15) Zee-Cheng, K.; Cheng, C. *J. Org. Chem.* **1962**, *27*, 976.

(16) Lee, J.; Paudler, W. *J. Heterocycl. Chem.* **1972**, *9*, 995.

solution was adjusted to pH 5.5 with glacial HOAc and extracted with $CHCl_3$ (4 × 50 mL). The $CHCl_3$ extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to a partially solid residue. The residue was triturated with Et_2O (10 mL). The white solid, **23**, was collected by filtration, washed with Et_2O, and dried under vacuum: yield 0.097 g (20%) after recrystallization from MeOH; mp 203–204 °C (lit. mp 201–203 °C). Anal. ($C_5H_7N_3O_2$). The aqueous layer (from the extraction) was concentrated under vacuum at 50 °C to a white solid. A mixture of this residue and 6 g of silica in MeOH was concentrated to dryness and added to a column (2.4 cm × 60 cm) of silica gel 60 (100 g, EM Reagents, 0.06–0.200 mm size) in EtOAc. Elution of the column with a 9:1 EtOAc/MeOH mixture gave **24**, which was subsequently recrystallized from toluene; yield 0.147 g (28%) obtained as colorless crystals of the hemihydrate; mp 103–104 °C (lit. mp 82 °C for nonhydrated form). Anal. ($C_6H_9N_3O{\cdot}0.5H_2O$).

(B) Acidic Conditions (24). A solution of **17a** (0.50 g, 2.74 mmol) in 96% HCOOH (8 mL)[11] was heated at reflux under nitrogen for 96 h and concentrated under vacuum to a yellow oil. After dissolution in H_2O (2 mL) and concentration under vacuum, the residue was dissolved in EtOAc (5 mL). A contaminant (neither **17a** nor **23**) was removed by filtration, and the solvent was removed under vacuum. The resulting partially crystalline residue was triturated with Et_2O (10 mL). The product was isolated by filtration: yield 0.34 g (75%), identified as **24** by comparison (NMR, UV, and TLC) with the sample described above.

Sodium 3-(1-Cyano-3,3,3-trifluoroacetonylidene)-2,6-dimethyl-1,2,4-triazin-5-olate (25a). Under nitrogen, trifluoroacetic anhydride[10] (1.52 mL, 11 mmol) was added dropwise to a stirred, cold (ice–MeOH bath) suspension of **17a** (1.82 g, 0.01 mol) in anhydrous THF (20 mL, freshly distilled from $LiAlH_4$ under N_2) and triethylamine (5.6 mL, 40 mmol, freshly distilled) at a rate that maintained the temperature below 5 °C. The cooling bath was removed, and stirring at ambient temperature was continued for 22.5 h. The orange-red mixture was concentrated under vacuum at 40 °C to a partially solid residue, which was dissolved in ice–water (20 g) and extracted with $CHCl_3$ (5 × 75 mL). The combined $CHCl_3$ layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to a dark oil. Dissolved in EtOAc (30 mL), the residue was applied to a column (2.4 cm × 60 cm) of silica gel 60 (100 g, EM Reagents) in EtOAc. The column was eluted with EtOAc (6 L). The desired product, found (as a wide band) in 4 L of solution, was obtained by removing the solvent under vacuum: yield 1.78 g; TLC (EtOAc), R_f 0.13. Recrystallization from EtOAc:toluene provided 0.942 g (33%): mp >300 °C; ^1H NMR (Me_2SO-d_6) 2.10 (s, 3 H) 3.57 (s, 3 H); ^{13}C NMR (D_2O) ppm (reference dioxane) 19.23 s (6-Me), 47.13 s (N-CH_3), 73.28 s (α-C) 121.03 q (CF_3, J = 288.7 Hz), 123.24 s (CN), 155.23 s (C-6), 162.13 s (C-3 or C-5), 167.15 s (C-5 or C-3), 173.09 (O=CCF_3); mass spectrum (70 eV, 270 °C), m/z 282 (2.0%) with accurate mass 282.0337 ($C_9H_6F_3N_4NaO_2$); mass spectrum (field-desorption) 283 (M + H), 282 (M); UV (MeOH) λ_{max} 245 nm (ϵ 21 200), 306 (12 400); IR (nujol) 2225 cm^{-1} (CN). Anal. Calcd for $C_9H_6F_3N_4NaO_2$: C, 38.31; H, 2.14; N, 19.86; Na, 8.15. Found: C, 38.37; H, 2.14; N, 19.73; Na, 8.05.

Sodium 3-(1-Cyano-3,3,3-trifluoroacetonylidene)-2-methyl-6-phenyl-1,2,4-triazin-5-olate (25b). Under nitrogen, to a vigorously stirred suspension of **17b** (0.61 g, 2.5 mmol) and triethylamine (1.01 g, 10 mmol) in anhydrous THF (10 mL) at −5 °C was added trifluoroacetic anhydride[10] (0.75 mL) at such a rate that the temperature did not exceed −3 °C. The cooling bath was removed, and stirring was continued at ambient temperature for 4 h. The resulting red solution was concentrated under vacuum to an orange syrup which was treated with H_2O (10 mL). The mixture was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were washed with saturated NaCl (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to an orange gum. A solution of the gum in EtOAc (10 mL) was subjected to preparative HPLC on silica conditioned with EtOAc. The product eluted as a broad band beginning near the solvent front. The fraction containing **25b** was concentrated to 10 mL and chilled. The colorless crystals were collected by filtration and dried under vacuum (70 °C): yield 0.39 g (44%); mp >300 °C; ^1H NMR (Me_2SO-d_6) δ 3.71 (s, 3 H), 7.41–7.50 (m, 3 H), 8.03–8.17 (m, 2 H); IR (nujol) 2220 cm^{-1} (CN); TLC (EtOAc), R_f 0.28. Anal. Calcd for $C_{14}H_8N_4NaO_2F_3$: C, 48.85; H, 2.34; N, 16.28; Na, 6.68. Found: C, 48.79; H, 2.48; N, 16.06; Na, 6.42.

2-(2,5-Dihydro-2,6-dimethyl-5-oxo-1,2,4-triazin-3-yl)-4,4,4-trifluoro-3-oxobutyronitrile (26). To **25a** (2.95 g, 10.4 mmol) was added 0.1 N HCl (105 mL). A flocculent solid formed. The mixture was stirred briefly (3–4 min) at room temperature and filtered. The solid was washed with H_2O (2 × 5 mL) and dried under vacuum (25 °C): yield, 2.47 g that upon recrystallization from Et_2O provided 2.15 g (80%) of **26** as colorless crystals; mp 144–145 °C; ^1H NMR (Me_2SO-d_6) δ 2.20 (s, 3 H), 3.72 (s, 3 H), 7.95 (br, solvent H_2O and exchangeable CH); UV (MeOH) λ_{max} 232 nm (ϵ 15 300), 317 (12 800); IR (nujol) 2210 (CN), 1727 cm^{-1} (C=O); IR (KBr) 2210, 1720 cm^{-1}; mass spectrum (70 eV, 100 °C), m/z 260 (M, 35%), 192 (10), 191 (100), 150 (20), 107 (23) 83 (17), 79 (12), 69 (16), 67 (11), 42 (31); TLC (EtOAc:MeOH/4:1), R_f 0.53. Anal. Calcd for $C_9H_7F_3N_4O_2$: C, 41.55; H, 2.71; N, 21.54. Found: C, 41.51; H, 2.72; N, 21.53.

3-(Cyanomethyl)-2,6-dimethyl-1,2,4-triazin-5(2*H*)-one (27). A solution of **25a** (243 mg, 0.86 mmol) in H_2O (3 mL) was treated with 1.0 N HCl (1.0 mL). A voluminous precipitate formed. The mixture was allowed to stand in a stoppered flask at room temperature for seven days. Most of the solid dissolved by the second day and none remained after a week. The yellow solution was neutralized with 1.0 NaOH (1.0 mL) and extracted with $CHCl_3$ (4 × 20 mL). The combined $CHCl_3$ layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to a white powder that was subsequently recrystallized from toluene: yield 96 mg (68%); mp 139–140 °C; NMR (Me_2SO-d_6) δ 2.14 (s, 3 H), 3.68 (s, 3 H), 4.43 (s, 2 H); UV (MeOH) λ_{max} 248.5 nm (ϵ 12 400), 260 sh (10 000); IR 2260 cm^{-1} (CN); TLC (EtOAc), R_f 0.18. Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.07; H, 4.99; N, 34.04.

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Registry No. **1a**, 29939-37-5; **1b**, 94295-29-1; **1c**, 94295-28-0; **2**, 517-21-5; **3**, 94295-30-4; **4**, 94295-31-5; **5**, 34122-01-5; **6**, 94295-32-6; **7**, 21141-03-7; **8**, 1074-12-0; **9a**, 94295-36-0; **9b**, 94295-35-9; **13**, 94295-33-7; **14**, 600-22-6; **15**, 1603-79-8; **16a**, 94295-37-1; **16b**, 94295-34-8; **16c**, 94295-38-2; **16d**, 94295-39-3; **17a**, 94295-43-9; **17b**, 94295-42-8; **17c**, 94295-41-7; **20**, 94295-40-6; **21**, 94295-44-0; **22**, 94295-45-1; **23**, 62764-55-0; **24**, 39070-04-7; **25a**, 94295-46-2; **25b**, 94295-47-3; **26**, 94295-48-4; **27**, 94295-49-5; EtOH, 64-17-5; H_2O, 7732-18-5; CF_3COOH, 76-05-1; NaOH, 1310-73-2; MeOH, 67-56-1; THF, 109-99-9; HCOOH, 64-18-6; 4-chloropyrimidin-6(1*H*)-one, 4765-77-9; benzylhydrazine dihydrochloride, 20570-96-1; triethylamine, 121-44-8; methylhydrazine, 60-34-4; sodium bisulfite, 7631-90-5; zinc, 7440-66-6; 2,3-butanedione, 431-03-8; palladium hydroxide, 63310-18-9; carbon, 7440-44-0; trifluoroacetic anhydride, 407-25-0.

Supplementary Material Available: Microanalyses, UV, and NMR for compounds **1b**, **7**, **9a**,**b**, **16a**,**c**, **17c**, **23**, and **24**, and mass spectra on **7**, **9a**, **23**, and **24** (5 pages). Ordering information is given on any current masthead page.