Guanine, Hypoxanthine, and Xanthine Analogues. Synthesis of Imidazo[1,5-*a*]-1,3,5-triazinones via Rearrangement

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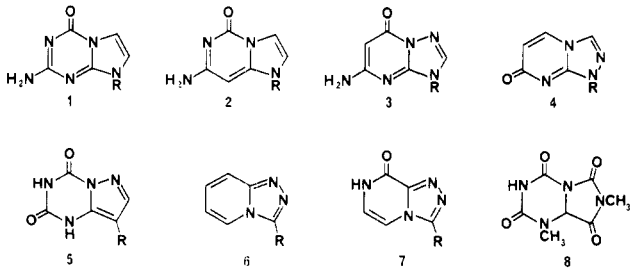
Syntheses of substituted imidazo[1,5-*a*]-1,3,5-triazinones, which are analogues of N(9)-substituted guanines, hypoxanthines, and xanthines, have been accomplished by cyclization–rearrangement. Condensation of ethyl 2-cyano-2-formamidopropionate and ethyl 2-acetamido-2-cyanopropionate with urea, thiourea, guanidine, and N^1,N^1-dimethylguanidine yielded substituted 4,5-dihydro-5-methylpyridin-4-ones. Treatment of these 4,5-dihydro-5-methylpyrimidin-4-ones with chlorotrimethylsilane and hexamethyldisilazane in pyridine gave the correspondingly substituted imidazo[1,5-*a*]-1,3,5-triazinones. Structures were established in this series on the basis of precursors and routes of synthesis, ^{1}H and ^{13}C NMR spectra, and mass spectra and by X-ray crystallographic analysis of one member among the interrelated compounds in the series.

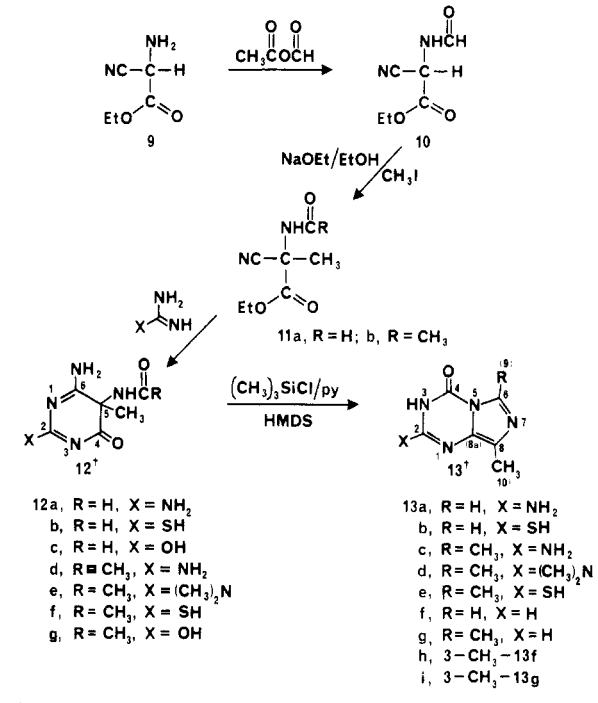
The synthesis and biological evaluation of analogues of the naturally occurring nucleic acid bases and their corresponding nucleosides, nucleotides, and coenzymes are directed toward defining those chemical interactions involved in the effecting or preventing of a specific biological response. In contrast to the successful syntheses of innumerable purine base analogues which contain a ring-juncture nitrogen,[1] the documentation of the syntheses of *N*-glycosyl nucleosides of this type has been limited to the cases of the imidazo[1,2-*a*]-1,3,5-triazine (e.g., **1**),[2,3] imi-



dazo[1,2-*c*]pyrimidine (e.g., **2**),[4,5] *s*-triazolo[1,5-*a*]pyrimidine (e.g., **3**),[6,7] and *s*-triazolo[4,3-*a*]pyrimidine (e.g., **4**)[8] ring systems. In addition, the syntheses of a few bridgehead-nitrogen bearing *C*-glycosyl nucleosides, derived from pyrazolo[1,5-*a*]-1,3,5-triazines (e.g., **5**),[9] *s*-triazolo[4,3-*a*]-pyridines (e.g., **6**),[10] and *s*-triazolo[4,3-*a*]pyrazines (e.g., **7**),[11] have recently been published.

We have communicated an observed rearrangement which effectively leads to imidazo[1,5-*a*]-1,3,5-triazines, analogues of N(9)-substituted guanines, hypoxanthines, and xanthines,[12] and we now supply details indicative of the generality of this cyclization–rearrangement. Earlier reference to this heterocyclic system is limited to the reported preparation of compound 8 by Biltz,[13] in extension of Fischer's exploratory investigation of the chemical properties and reactivity of theobromine.[14] 5-Acetamido-6-amino-4,5-dihydro-5-methyl-2(3*H*)-thiopyrimidin-4-one (**12f**) was a pivotal intermediate in our synthesis (Scheme I). The closure to an imidazo ring, on the basis of the work of Vorbrüggen involving the amination of *O*-trimethylsilylated heterocycles,[15] resulted in the corresponding imidazo[1,5-*a*]-1,3,5-triazine **13e** as a result of quaternary-carbon bond cleavage[16] and rear-

Scheme I



† The listings of R and X conveniently indicate substitution but do not necessarily indicate the favored tautomeric form.

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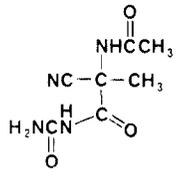
rangement. Raney nickel desulfurization in aqueous ammonia yielded 6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**13g**), the structure of which was established by single-crystal X-ray analysis inter alia as a representative of the entire series.

Results and Discussion

The condensation of disubstituted cyanoacetic esters with guanidine was shown very early to provide derivatives of 2,6-diamino-4,5-dihydropyrimidin-4-ones.[17] A synthetic route based on this precedent was adapted to the preparation of the 4,5-dihydropyrimidin-4-ones **12a,b,d–g** as shown in Scheme I. Ethyl 2-amino-2-cyanoacetate (**9**), prepared according to the method of Domkin and Kur'yanovich,[18] was formylated by treatment with acetic formic anhydride to give ethyl 2-cyano-2-formamidoacetate (**10**). Subsequent reaction of an ethanolic solution of **10** with methyl iodide in the presence of sodium ethoxide gave ethyl 2-cyano-2-formamidopropionate (**11a**). Condensation of **11a** or ethyl 2-acetamido-2-cyanopropionate (**11b**)[19] with guanidine, N^1,N^1-dimethylguanidine, or thiourea in ethanol containing 1–3 molar equiv of sodium ethoxide, followed by the addition of acetic acid to pH 5.5, yielded the corresponding 4,5-dihydropyrimidin-4-one derivatives **12a,b,d–f**.

The condensation of **11b** with urea requires conditions different from those employed in the cyclizations with guanidine, N^1,N^1-dimethylguanidine, and thiourea. Examination of the literature reveals that condensations of substituted α-cyano esters with urea in the presence of sodium ethoxide afford the acyclic cyanoacetylureas.[20] In the present case, *N*-(2-acetamido-2-cyanopropionyl)urea (**14**) was first formed and could be isolated and characterized by its ^{1}H NMR spectrum. Cyclization to the dihydropyrimidinone **12g** was accomplished by addition of acetic acid to pH 8.5. We assume that the lower homologue **12c** would also be obtainable from **11a** by a similar sequence.



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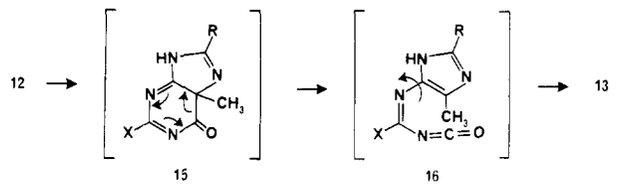
An efficient procedure for the closure to the imidazo ring to yield the imidazo[1,5-*a*]-1,3,5-triazines **13a–e** was based on the amination of *O*-trimethylsilylated heterocycles as reported by Vorbrüggen et al.[15] Treatment of the compounds **12a,b,d–f** in pyridine with 2 molar equiv of chlorotrimethylsilane and excess hexamethyldisilazane at reflux under nitrogen gave the imidazo[1,5-*a*]-1,3,5-triazines **13a–e**. The formamido derivatives **12a** and **12b** demonstrated a marked tendency toward this imidazole ring closure and rearrangement in contrast to the acetamido derivatives **12d–f**, which required prolonged heating at reflux to effect complete product formation. The sequence of events has not been established, but initial cyclization of a trimethylsilylated **12** to add an appended imidazole-type ring would thereby provide better stabilization for C(4)–C(5) cleavage (either heterolytically or electrocyclically) than would be provided before cyclization of the five-membered ring. One possible route of **12** to **13** would then result, e.g., from an electrocyclic conversion[21] of **15** to **16** (X is trimethylsilylated in all but **12e**) and



15 **16**

rotation about the original N(1)–C(6) bond (see numbering in **12**) to place the isocyanate grouping in juxtaposition to the original N^6 for closure to the resonance-stabilized ring system of **13**.

Whatever the detailed mechanistic pathway, the structures of the resulting rearrangement products (**13**) were firmly established by interconversion, analogy, spectroscopic data, and X-ray analysis. For example, Raney nickel desulfurization of compound **13e** in aqueous ammonia gave **13g**. A single crystal of **13g** of suitable dimensions for X-ray analysis[12] was obtained by slow crystallization from 2-propanol. The crystal structure determination of compound **13g** (see Experimental Section) also confirmed the structure of the 8-methylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (**13f**) product of Raney nickel disulfurization of **13b**. The ^{1}H NMR spectra of the dimethyl (**13g**) and monomethyl (**13f**) compounds showed parallel chemical shifts for the 8-CH_3 and 2-H resonances, differing in the 6-CH_3 chemical shift, δ 2.65, for **13g** and the 6-H shift, δ 8.18, for **13f**. The structures of the dimethyl and monomethyl thio compounds, **13e** and **13b**, respectively, were thus established since they were the precursors of **13g** and **13f**. The ^{13}C NMR spectra of **13e** and **13g** were confirmatory for the lack of any tetrasubstituted carbon in this set of compounds. This was also true for **13a** and **13d** (see below), which, along with **13c**, are structurally related, substituted imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones, as supported by other spectroscopic criteria.

Further structural verification resulted from a chemical reaction that was diagnostic of the 3,4-amide unit in **13g** and **13f**. Žemlička[22] has shown that 1,1-dimethoxy-*N*,*N*-dimethylmethanamine, or *N*,*N*-dimethylformamide dimethyl acetal, alkylates heterocyclic bases at amide nitrogens when no free amino groups are present. With this reagent, it was possible to convert compound **13g** to 3,6,8-trimethylimidazo[1,5-*a*]-1,3,5-triazin-4-one (**13i**), with ^{1}H NMR δ 3.43 for the new NCH_3 protons, and **13f** to 3,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4-one (**13h**), with δ 3.50 for the new NCH_3 protons.

The ^{13}C NMR spectra of compounds **12a,d–f** and **13a,d,e,g** are consistent with the structures as illustrated. Positions of appropriate chemical shift values clearly demonstrate the presence of a tetrasubstituted carbon prior to conversion of the substituted 4,5-dihydropyrimidin-4-ones to the corresponding imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones. For example, 5-acetamido-6-amino-4,5-dihydro-2-(dimethylamino)-5-methylpyrimidin-4-one (**12e**) shows four signals between 164 and 179 ppm corresponding to C(2), C(4), C(6), and the acetyl carbonyl carbon; signals at 22.4, 26.0, and 36.9 ppm are due to the 5-CH_3, $COCH_3$, and $(CH_3)_2N$ methyl groups, respectively; and the crucial resonance at 53.4 ppm es-

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tablishes the presence of the tetrasubstituted C(5).[23] By contrast, the ^{13}C NMR spectrum of compound **13d**, the cyclization–rearrangement product of **12e**, confirms the absence of a tetrasubstituted carbon. Similarly, the ^{13}C NMR spectra of compounds **12a,d,f** possess resonances characteristic of carbon tetrasubstitution (54.4–62.6 ppm) while compounds **13a,e,g** lack resonances indicative of the presence of a quaternary carbon.

Analysis of the major fragment ions in the mass spectra determined at 10 eV for the 4,5-dihydropyrimidin-4-one and imidazo[1,5-a]-1,3,5-triazin-4-one derivatives revealed common features between and within each series. The mono- and bicyclic heterocycles characteristically showed a predominant molecular ion, with compound **12g** being the only exception (relative abundance for $M^+ = 14$). Each of the 4,5-dihydropyrimidin-4-one derivatives **12** fragmented with the loss of the neutral HNCO ($M^+ - 43$), with the exception of **12f**, which lost HNCS. The losses of NH_3, H_2O, and CO were evident in the fragmentations recorded for each of the 4,5-dihydro-5-formamidopyrimidin-4-one derivatives. The imidazo[1,5-a]-1,3,5-triazin-4-one fragmentation patterns exhibit some decomposition losses in common, and each of the 2-aminoimidazo[1,5-a]-1,3,5-triazin-4-ones **13a,c,d** show the loss of the C(2)–N(3) fragment, i.e., H_2NCN or $(CH_3)_2NCN$.

Examination of the ^1H NMR spectra obtained in a common solvent for the 8-methylimidazo[1,5-a]-1,3,5-triazin-4-ones **13a,b,f,h** and the corresponding 6,8-dimethylimidazo[1,5-a]-1,3,5-triazin-4-ones **13c,e,g,i** establishes a relationship between the chemical shift value of the C(8) methyl hydrogens and the presence of a methyl group at the C(6) position. In each case, the replacement of the C(6) hydrogen of the imidazo[1,5-a]-1,3,5-triazin-4-one with a methyl substituent resulted in a 0.10-ppm upfield shift in the observed C(8) methyl hydrogen resonance. In close comparison, 4-methylimidazole exhibits a methyl hydrogen resonance at δ 2.27, and the ^1H NMR spectrum of 2,4-dimethylimidazole shows a resonance at δ 2.21 corresponding to the 4-methyl hydrogens.

The analogy between C(8) substitution in **13a** and **13f**, as examples, and N(9) substitution on guanine and hypoxanthine, respectively, suggests further applications of the observed cyclization–rearrangement sequence. Synthetic approaches to imidazo[1,5-a]-1,3,5-triazines which permit incorporation of a C(8) ribosyl unit or an analogous moiety are currently under investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on JEOL FX-60, Varian A-60, EM-390, and/or HA-100 spectrometers employing tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained on a Varian MAT CH-5 spectrophotometer. Field-desorption and high-resolution mass spectra were obtained on a Varian MAT 731 spectrophotometer, coupled with a 620i computer and a STATOS recorder. The ultraviolet spectra were obtained on a Beckman Acta Model M VI spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for quantitative ultraviolet absorption spectra. The pyridine used in the reactions described below was distilled from barium oxide and stored over calcium hydride prior to use. Thin-layer chromatography was carried out on EM silica gel f-254 plates (thickness 0.25 mm). The solvent systems employed were chloroform–ethanol (9:1 to 4:1, v/v) and isobutyric acid–H_2O–NH_4OH (75:24:1, v/v). Brinkman 0.05–0.2-mm silica gel was used for column chromatography.

Ethyl 2-Cyano-2-formamidoacetate (10). Ethyl isonitrosocyanoacetate (20.0 g, 141 mmol) was reduced to **9** with sodium dithionite according to the method of Domkin and Kur'yanovich.[18] Acetic formic anhydride[24] (13.6 g, 155 mmol) was added dropwise to a cooled (5 °C) solution of the aminocyano ester in ether (100 mL), the solution was stirred magnetically at room temperature for 2 h, solvent was removed in vacuo, and excess acid was coevaporated with toluene under reduced pressure to give a yellow oil which crystallized on scratching. Two recrystallizations from ether gave **10** as fine, long, colorless needles (8.3 g, 38%): mp 61–62 °C; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3, J = 6 Hz, CH_3), 4.33 (q, 2, J = 6 Hz, CH_2), 5.50 (d, 1, J = 8 Hz, 2-H), 7.18 (d, 1, J = 8 Hz, NH), 8.28 (s, 1, CHO).

Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.31; H, 5.23; N, 17.94.

Ethyl 2-Cyano-2-formamidopropionate (11a). To a solution of sodium ethoxide (2.30 g of Na in 75 mL of absolute ethanol, 100 mmol) was added **10** (15.6 g, 100 mmol) followed by iodomethane (16.9 g, 120 mmol). The resulting solution was heated at reflux for 30 min and cooled. Solvent was removed in vacuo to give an oily residue which was dissolved in 35 mL of water, extracted with chloroform, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 14.6 g (86%) of product as a white solid of sufficient purity for further transformations: mp 61–62 °C (recrystallized from ether); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, J = 6 Hz, CH_3), 1.89 (s, 3, 2-CH_3), 4.30 (q, 2, J = 6 Hz, CH_2), 7.48 (br, 1, NH), 8.20 (s, 1, CHO).

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.08; H, 5.88; N, 16.27.

Ethyl 2-Acetamido-2-cyanopropionate (11b).[19] To a solution of sodium ethoxide (1.35 g of Na in 200 mL of absolute ethanol, 58.8 mmol) was added ethyl 2-acetamido-2-cyanoacetate (10.0 g, 58.8 mmol) followed by iodomethane (11.9 g, 83.8 mmol). The resulting solution was heated at reflux for 1 h and cooled, and the solvent was removed in vacuo to give an oily residue. This was dissolved in 20 mL of water and extracted with dichloromethane (3 × 20 mL), and the dichloromethane solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to give a white solid. Recrystallization from benzene (substitute ethanol or ethyl acetate) gave **11b** as white needles (10.2 g, 94%): mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, CH_3), 1.81 (s, 3, 2-CH_3), 2.06 (s, 3, $COCH_3$), 4.24 (q, 2, J = 7 Hz, CH_2), 7.45 (s, 1, NH).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.53; N, 6.09. Found: C, 52.10; H, 6.58; N, 5.85.

2,6-Diamino-4,5-dihydro-5-formamido-5-methylpyrimidin-4-one (12a). A solution of sodium ethoxide (0.92 g of Na in 25 mL of absolute ethanol, 40 mmol) was treated with guanidinium carbonate (1.80 g, 10 mmol), stirred magnetically at room temperature for 30 min, filtered into an ethanolic solution of **11a** (3.40 g in 10 mL of absolute ethanol, 20 mmol), and stirred overnight. The white precipitate formed on neutralization with acetic acid was collected by filtration and washed with water followed by ethanol to give homogeneous **12a** (3.10 g, 83%): mp 235 °C dec (recrystallized from water); UV λ_{max} (EtOH) 234 nm (ϵ 20 500), 271 (8600); ^1H NMR (CF_3CO_2H) δ 2.02 (s, 3, CH_3), 8.34 (s, 1, CHO), 8.50 (s, 1, NHCO); ^{13}C NMR (CF_3CO_2H, D_2O) δ 62.6 (C(5)); MS m/e (rel abundance; 10 eV) 183 (M^+, 99), 166 (50), 165 ($M^+ - H_2O$, 33), 155 ($M^+ - CO$, 54), 154 (31), 141 (25), 140 ($M^+ - HNCO$, 42), 138 (100), 137 (71), 112 (99), 86 (95), 70 (23), 69 (29), 43 (21), 42 (NCO^+, 20).

Anal. Calcd for $C_6H_9N_5O_2 \cdot {}^1/_2H_2O$: C, 37.58; H, 5.23; N, 36.52. Found: C, 37.37; H, 5.25; N, 36.49.

6-Amino-4,5-dihydro-5-formamido-5-methyl-2(3*H*)-thiopyrimidin-4-one (12b). To a solution of sodium ethoxide (0.05 g of Na in 4 mL of absolute ethanol, 2.2 mmol) were added thiourea (0.15 g, 2.0 mmol) and a solution of **11a** (0.34 g in 2 mL of absolute ethanol, 2.0 mmol). The resulting solution was stirred at room temperature for 28 h, adjusted to pH 5.5 with glacial acetic acid, and kept at 5 °C for 12 h. Upon sodium acetate removal via filtration and filtrate maintenance at 5 °C for 1 week, yellow crystals of homogeneous **12b** were obtained (0.10 g). Concentration of the filtrate in vacuo and addition of water (1 mL) gave an

(23) For representative ^{13}C NMR chemical shift values, see: Johnson, L. F.; Jankowski, W. C. "Carbon-13 NMR Spectra"; Wiley-Interscience: New York, 1972.

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additional 0.03 g (0.13 g total, 32%): mp 240 °C dec (recrystallized from water); UV λ_{max} (EtOH) 261 nm (ϵ 8300), 317 (6000); ^{1}H NMR ($(CD_3)_2SO$) δ 1.52 (s, 3, CH_3), 7.93 (s, 1, CHO), 8.60 (br, 2, NH_2), 9.20 (br, 1, N(3)H), 11.60 (br, 1, NHCO); MS m/e (rel abundance; 10 eV) 200 (M^+, 100), 183 (3), 182 ($M^+ - H_2O$, 7), 172 ($M^+ - CO$, 11), 157 ($M^+ - HNCO$, 15), 155 (13), 139 (21), 131 (14), 42 (NCO^+, 31).

Anal. Calcd for $C_6H_8N_4O_2S$: C, 36.00; H, 4.03; N, 27.99; S, 15.92. Found: C, 36.03; H, 4.00; N, 27.90; S, 15.90.

5-Acetamido-2,6-diamino-4,5-dihydro-5-methylpyrimidin-4-one (12d). A solution of sodium ethoxide (0.46 g of Na in 15 mL of absolute ethanol, 20 mmol) was treated with guanidinium carbonate (0.90 g, 5 mmol), stirred magnetically at room temperature for 1 h, filtered into an ethanolic solution of **11b** (1.84 g in 20 mL of absolute ethanol, 10 mmol), and heated at reflux for 1.5 h. After the solution had cooled, it was neutralized with acetic acid, causing precipitation of **12d**. The precipitate was collected by filtration and washed with water and ethanol to give homogeneous **12d** as a white solid (1.40 g, 71%): mp 256 °C dec (recrystallized from water); UV λ_{max} (EtOH) 234 nm (ϵ 15 800), 269 (7100); ^{1}H NMR (CF_3CO_2H) δ 1.97 (s, 3, CH_3), 2.29 (s, 3, $COCH_3$), 8.30 (s, 1, NHCO); ^{13}C NMR (CF_3CO_2H, D_2O) 58.6 (C(5)); MS m/e (rel abundance; 10 eV) 197 (M^+, 100), 180 (6), 179 ($M^+ - H_2O$, 12), 169 ($M^+ - CO$, 5), 155 (20), 154 ($M^+ - HNCO$, 100), 138 (94), 137 (87), 112 (14), 86 (57), 69 (41), 43 (CH_3CO^+, 100).

Anal. Calcd for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.33; H, 5.82; N, 35.22.

5-Acetamido-6-amino-4,5-dihydro-2-(dimethylamino)-5-methylpyrimidin-4-one (12e). To a solution of sodium ethoxide (127 mg of Na in 50 mL of absolute ethanol, 5.5 mmol) was added N^1,N^1-dimethylguanidine hydrochloride (688 mg, 5.4 mmol), and the mixture was stirred at room temperature for 5 min. **11b** (1.0 g, 5.4 mmol) was added, and the mixture was heated at reflux for 35 min. After the addition of ether (25 mL), a solid material was collected by filtration. Recrystallization from aqueous ethanol gave **12e** as a white powder (610 mg, 50%): mp 245–246 °C dec; UV λ_{max} (EtOH) 260 nm (ϵ 23 500); ^{1}H NMR ($(CD_3)_2SO$) δ 1.28 (s, 3, 5-CH_3), 1.79 (s, 3, $COCH_3$), 3.02 (s, 3, CH_3N), 3.12 (s, 3, CH_3N), 7.69 (s, 1, NH), 7.84 (s, 1, NH), 8.34 (s, 1, NHCO); ^{13}C NMR ($CDCl_3$) δ 22.4 (5-CH_3), 26.0 ($COCH_3$), 53.4 (C(5)), 164.5, 169.1, 177.5, 178.7; MS m/e (rel abundance; 10 eV) 225 (M^+, 72), 182 ($M^+ - HNCO$, 100), 140 (9), 139 (11), 138 (8), 114 (19), 112 (13).

Anal. Calcd for $C_9H_{15}N_5O_2 \cdot H_2O$: C, 44.43; H, 7.04; N, 28.79. Found: C, 44.65; H, 7.05; N, 28.79.

5-Acetamido-6-amino-4,5-dihydro-5-methyl-2(3*H*)-thiopyrimidin-4-one (12f). To a solution of sodium ethoxide (4.6 g of Na in 300 mL of absolute ethanol, 200 mmol) was added **11b** (12.3 g, 66 mmol) followed by thiourea (5.1 g, 66 mmol). The resulting solution was heated at reflux for 1 h, cooled to 5 °C, and adjusted to pH 5.5 with 10% aqueous acetic acid, causing deposition of homogeneous **12f** as yellow crystals (7.3 g, 54%): mp 243 °C dec (recrystallized from water); UV λ_{max} (EtOH) 261 nm (ϵ 8270), 317 (6600); ^{1}H NMR ($(CD_3)_2SO$, D_2O) δ 1.44 (s, 3, 5-CH_3), 1.85 (s, 3, $COCH_3$); ^{13}C NMR ($(CD_3)_2SO$) δ 21.5 (5-CH_3), 24.2 ($COCH_3$), 54.4 (C(5)), 168.6, 170.0, 172.2, 187.2 (CS); MS m/e (rel abundance; 10 eV) 214 (M^+, 100), 155 ($M^+ - HNCS$, 30), 143 (15).

Anal. Calcd for $C_7H_{10}N_4O_2S \cdot H_2O$: C, 36.21; H, 5.21; N, 24.13; S, 13.78. Found: C, 36.18; H, 5.11; N, 23.88; S, 13.76.

Concentration of the filtrate yielded additional **12f** (12%) and another component (6%), subsequently identified as **13e** (see below).

5-Acetamido-6-amino-4,5-dihydro-5-methylpyrimidine-2,4(3*H*)-dione (12g). To a solution of sodium ethoxide (205 mg of Na in 20 mL of absolute ethanol, 8.9 mmol) was added **11b** (498 mg, 2.7 mmol) followed by urea (175 mg, 2.9 mmol). The resulting solution was stirred at room temperature for 4 h and adjusted to pH 8.5 with acetic acid. Subsequent to the addition of acid, a precipitate formed which was collected by centrifugation. The precipitate was washed with absolute ethanol (5 mL), collected by centrifugation, and heated in vacuo at 100 °C (0.025 mm) for 12 h to give homogeneous **12g** as a white solid (262 mg, 49%): mp 255 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 1.50 (s, 3, CH_3), 1.87 (s, 3, $COCH_3$), 8.07 (br, 3, NH's), 8.67 (s, 1, NHCO); MS m/e (rel abundance; 10 eV) 198 (M^+, 14), 180 ($M^+ - H_2O$, 3), 156 (18), 155 ($M^+ - HNCO$, 42), 137 (23), 113 (100), 112 (32), 85 (11), 43 (27), 42 (NCO^+, 32).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.52; H, 4.97; N, 28.28.

If at the stage of the addition of acetic acid the pH was adjusted immediately to 5.5, a precipitate was formed which was collected by centrifugation and was identifiable by ^{1}H NMR analysis as *N*-(2-acetamido-2-cyanopropionyl)urea (**14**): δ 1.70 (s, 3, CH_3), 1.86 (s, 3, $COCH_3$), 7.34 (br, 2, NH_2), 8.90 (s, 1, $NHCOCH_3$), 10.03 (br, 1, CONHCO).

2-Amino-8-methylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13a). A suspension of **12a** (1.83 g, 10 mmol), dry pyridine (40 mL), and chlorotrimethylsilane (2.17 g, 20 mmol) was stirred at room temperature for 30 min. After hexamethyldisilazane (3.23 g, 20 mmol) was added, the mixture was heated at reflux for 10 min. A white solid which separated from the cooled solution was collected by filtration, washed with anhydrous ethanol, and recrystallized from water to give an analytical sample of **13a** (759 mg, 46%): mp 220 °C dec; UV λ_{max} (EtOH) 267 nm (ϵ 8800); ^{1}H NMR ($(CD_3)_2SO$) δ 2.13 (s, 3, 8-CH_3), 6.23 (s, 2, NH_2), 7.78 (s, 1, 6-H); ^{13}C NMR ($(CD_3)_2SO$) δ 11.3 (8-CH_3), 119.0 (C(8)), 123.5 (C(6)), 144.5, 147.6, 149.0; MS m/e (rel abundance; 10 eV) 165 (M^+, 100), 164 (24), 123 (20), 122 ($M^+ - HNCO$, 7), 121 (7).

Anal. Calcd for $C_6H_7N_5O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.39; H, 4.14; N, 42.32.

8-Methyl-2(1*H*)-thioimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13b). A suspension of **12b** (0.27 g, 1.4 mmol), dry pyridine (5 mL), and chlorotrimethylsilane (0.30 g, 2.8 mmol) was stirred at room temperature for 30 min. Hexamethyldisilazane (0.42 mL, 2.0 mmol) was added, and the mixture was heated at reflux for 10 min. The crystalline precipitate was collected by filtration, stirred with anhydrous ethanol (3 mL) for 5 min, collected by filtration, washed with cold absolute ethanol (5 mL), and heated in vacuo at 100 °C (0.025 mm) for 8 h to remove ammonium chloride, thus giving homogeneous **13b** (210 mg, 85%): mp 242 °C dec (recrystallized from water); UV λ_{max} (EtOH) 240 mm (ϵ 7800), 299 (14 800); ^{1}H NMR ($(CD_3)_2SO$) δ 2.20 (s, 3, 8-CH_3), 8.00 (s, 1, 6-H), 12.20 (br, 2, NH); MS m/e (rel abundance; 10 eV) 182 (M^+, 100), 138 ($M^+ - CS$, 9), 137 (7), 114 (9), 96 (12), 86 (15).

Anal. Calcd for $C_6H_6N_4OS$: C, 39.56; H, 3.32; N, 30.76; S, 17.57. Found: C, 39.52; H, 3.32; N, 30.87; S, 17.35.

2-Amino-6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13c). A suspension of **12d** (985 mg, 5 mmol), dry pyridine (20 mL), and chlorotrimethylsilane (1.09 g, 10 mmol) was stirred at room temperature for 1 h. Hexamethyldisilazane (1.62 g, 10 mmol) was added, and the mixture was heated at reflux for 2 h. A crystalline precipitate, which separated upon cooling, was collected by filtration and washed with absolute ethanol (5 mL) to give 0.70 g of a trimethylsilylated derivative of **13c**. Hydrolysis of the silylated material (100 mg, 0.40 mmol) by heating in water (50 mL) at reflux for 10 min, cooling of the mixture, and collection of the resulting homogeneous tan solid gave **13c** (54 mg, 75%): mp 220 °C dec; UV λ_{max} (EtOH) 269 nm (ϵ 8600); ^{1}H NMR ($(CD_3)_2SO$) δ 2.03 (s, 3, 8-CH_3), 2.56 (s, 3, 6-CH_3), 6.28 (br, 2, NH_2); MS m/e (rel abundance; 10 eV) 179 (M^+, 100), 137 (67), 136 ($M^+ - HNCO$, 8); field-desorption mass spectrum, m/e 179 (M^+); high-resolution mass spectrum, m/e 179.0809 (calcd for $C_7H_9N_5O$).

Anal. Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 47.20; H, 5.15; N, 38.92.

2-(Dimethylamino)-6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13d). A suspension of **12e** (5.0 g, 22.4 mmol), dry pyridine (30 mL), and chlorotrimethylsilane (5.0 g, 46 mmol) was stirred at room temperature for 15 min. After hexamethyldisilazane (30 mL) was added, the mixture was heated until all of the solid material had dissolved. After the mixture was cooled, the solvents were removed in vacuo, and acetone (30 mL) was added to the residue. The mixture was allowed to stand for 2 min, and the solid material was collected by filtration to give homogeneous **13d** (3.1 g, 67%): mp 210–220 °C dec (recrystallized from ethyl acetate); UV λ_{max} (CH_3CN) 278 nm (ϵ 8200); ^{1}H NMR ($(CD_3)_2SO$) δ 2.07 (s, 3, 8-CH_3), 2.58 (s, 3, 6-CH_3), 3.00 (s, 6, $(CH_3)_2N$); ^{13}C NMR ($(CD_3)_2SO$) δ 10.9 (8-CH_3), 15.6 (6-CH_3), 37.5 ($N(CH_3)_2$), 116.0 (C(8)), 133.0, 134.0, 146.8, 148.7; MS m/e (rel abundance; 10 eV) 207 (M^+, 100), 206 (13), 137 ($M^+ - (CH_3)_2N$, 15), 59 (48), 43 (27); field-desorption mass spectrum, m/e 207 (M^+);

high-resolution mass spectrum, *m/e* 207.1128 (calcd for $C_9H_{13}N_5O$).

The **picrate**, made from **13d** in ethyl acetate and recrystallized picric acid in ethanol, was recrystallized rapidly from methanol or acetone: yellow needles; mp 235–242 °C dec; UV λ_{max} (CH_3CN) 374 nm (ϵ 17 600), 257 (16 250); ^1H NMR ($(CD_3)_2SO$) δ 2.20 (s, 3, 8-CH_3), 2.89 (s, 3, 6-CH_3), 3.06 (s, 6, $(CH_3)_2N$), 8.56 (s, 2, aromatic H's).

Anal. Calcd for $C_{15}H_{16}N_8O_8$: C, 41.28; H, 3.68; N, 25.69. Found: C, 41.23; H, 3.64; N, 25.40.

6,8-Dimethyl-2(1*H*)-thioimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13e). A suspension of **12f** (2.57 g, 12 mmol), dry pyridine (40 mL), and chlorotrimethylsilane (2.60 g, 24 mmol) was stirred for 30 min at room temperature. Hexamethyldisilazane (13.6 mL, 64.5 mmol) was added, and the mixture was heated at reflux for 4 h. After the mixture was cooled, the solvents were removed in vacuo, the residue was treated with absolute ethanol (20 mL), and the mixture was kept at 5 °C for 15 min. The cream-colored precipitate that was collected by filtration was washed with absolute ethanol to give homogeneous **13e** (1.96 g, 83%): mp 241–242 °C dec (recrystallized from water); UV λ_{max} (EtOH) 264 (sh) (ϵ 9800), 289 (13 800); ^1H NMR ($(CD_3)_2SO$) δ 2.10 (s, 3, 8-CH_3), 2.50 (overlaps with $(CD_3)_2SO$, 3, 6-CH_3); ^{13}C NMR ($(CD_3)_2SO$) δ 11.0 (8-CH_3), 15.4 (6-CH_3), 114.0 (C(8)), 124.5 (C(6)), 137.7, 142.3, 170.3 (CS); MS *m/e* (rel abundance; 10 eV) 196 (M^+, 100), 153 (M^+ – HNCO, 9), 137 (M^+ – HNCS, 26), 110 (15), 42 (NCO^+, 10).

Anal. Calcd for $C_7H_8N_4OS$: C, 42.84; H, 4.11; N, 28.55; S, 16.34. Found: C, 42.87; H, 4.03; N, 28.56; S, 16.29.

8-Methylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13f). A solution of **13b** (146 mg, 8 mmol), concentrated aqueous ammonia (3 mL), and moist Raney nickel catalyst (520 mg) was heated at reflux for 15 min. After removal of a pale green contaminant from the reaction mixture surface, the catalyst was removed by filtration and thoroughly washed with water. The residue obtained upon concentration of the filtrate in vacuo was subjected to column chromatography on silica gel (2 g) with ethanol–chloroform (1:4) as eluant to give an analytical sample of **13f** as white crystals (76 mg, 63%): mp 240 °C dec; UV λ_{max} (EtOH) 265 nm (ϵ 7600), 292 (sh) (3600); ^1H NMR ($(CD_3)_2SO$) δ 2.27 (s, 3, CH_3), 7.58 (s, 1, 2-H), 8.18 (s, 1, 6-H); MS *m/e* (rel abundance; 10 eV) 150 (M^+, 100), 149 (15), 123 (M^+ – HCN, 34), 122 (M^+ – CO, 10), 107 (M^+ – HNCO, 13), 96 (12).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.78; H, 4.03; N, 37.25.

6,8-Dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13g). A solution of **13e** (1.96 g in 30 mL of water, 10 mmol), concentrated aqueous ammonia (3 mL), and moist Raney nickel (6.5 g) was heated at reflux for 20 min. After a pale green contaminant was removed from the reaction mixture surface, the catalyst was removed by filtration and thoroughly washed with water. The filtrate was concentrated in vacuo and coevaporated with absolute ethanol (20 mL) under reduced pressure. The yellow residue (1.5 g) was treated with cold methanol to give a chromatographically homogeneous solid, **13g** (470 mg), an orange solution containing additional **13g**, and a less polar component. The solution was concentrated in vacuo, and the residue was subjected to column chromatography on silica gel (30 g) with ethanol–chloroform (1:4) as eluent to give 410 mg of additional **13g** (880 mg total, 53%): mp 269–270 °C dec (recrystallized from acetone); UV λ_{max} (EtOH) 263 nm (sh) (ϵ 4200), 267 (4300), 294 (sh) (1700); ^1H NMR ($(CD_3)_2SO$) δ 2.17 (s, 3, 8-CH_3), 2.65 (s, 3, 6-CH_3), 7.42 (s, 1, 2-H), 11.65 (br, 1, NH); ^{13}C NMR ($(CD_3)_2SO$) δ 11.0 (8-CH_3), 15.8 (6-CH_3), 124.6, 133.0, 136.9, 138.2 (C(2)), 144.8; MS *m/e* (rel abundance; 10 eV) 164 (M^+, 100), 137 (M^+ – HCN, 59), 136 (M^+ – CO, 7), 110 (9), 109 (10), 68 (11).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.05; H, 4.87; N, 34.32.

A single crystal for X-ray analysis was obtained by slow crystallization from 2-propanol.

3,8-Dimethylimidazo[1,5-*a*]-1,3,5-triazin-4-one (13h). A suspension of **13f** (60 mg in 10 mL of chloroform, 4.0 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.0 mL, 7.5 mmol) was kept at 60 °C for 12 h. The residue obtained upon concentration in vacuo was washed with anhydrous ether (1 mL) followed by sublimation at 77 °C (0.05 mm) to give homogeneous **13h** (35 mg, 53%): mp 192 °C dec (recrystallized from ethyl acetate); UV λ_{max} (EtOH) 267 nm (ϵ 9600), 294 (sh) (4400); ^1H NMR ($CDCl_3$) δ 2.40 (s, 3, 8-CH_3), 3.50 (s, 3, 3-CH_3), 7.25 (s, 1, 2-H), 8.13 (s, 1, 6-H); MS *m/e* (rel abundance; 10 eV) 164 (M^+, 100), 163 (11), 136 (M^+ – CO, 2), 123 (M^+ – C_2H_3N, 20), 107 (M^+ – CH_3NCO, 11), 42 (NCO^+, 19).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.09; H, 4.89; N, 34.23.

3,6,8-Trimethylimidazo[1,5-*a*]-1,3,5-triazin-4-one (13i). A suspension of **13g** (66 mg, 0.44 mmol) in 10 mL of chloroform and *N,N*-dimethylformamide dimethyl acetal (0.8 mL, 6 mmol) was kept at 60 °C for 7 h. Following solvent removal in vacuo, sublimation of the resulting yellow solid at 80 °C (7 mm) gave **13i** as white needles (33 mg, 42%): mp 130–132 °C (recrystallized from ether); UV λ_{max} (EtOH) 266 nm (sh) (ϵ 7600), 270 (7800), 294 (sh) (3200); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3, 8-CH_3), 2.80 (s, 3, 6-CH_3), 3.43 (s, 3, 3-CH_3), 7.25 (s, 1, 2-H); MS *m/e* (rel abundance; 10 eV) 178 (M^+, 100), 138 (5), 137 (M^+ – C_2H_3N, 72), 136 (9), 109 (8).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.45. Found: C, 53.90; H, 5.70; N, 31.47.

X-Ray analysis of 6,8-dimethylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-one (13g) has been reported in our earlier communication.

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Supplementary Material Available: A listing of fractional atomic coordinates (Table I), final thermal parameters (Table II), complete bond lengths and bond angles (Table III), and torsion angles (Table IV) (4 pages). Ordering information is given on any current masthead page.