Notes

Reactions of 6-Aminopyrimidines with Biselectrophiles: Manipulation of Product Composition with Solvent and Pyrimidine Substitution Variation[1]

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Received July 28, 1997

The one-step assembly of monocyclic as well as polycyclic heterocycles represents a useful strategy in contemporary organic synthesis. Such reactions are of special interest in combinatorial chemistry,[2] since this allows the generation of vast arrays of molecules (depending on the substitution on the reactants) in an efficient manner. We have reported the regiospecific synthesis of a number of bicyclic and tricyclic as well as tetracyclic heterocycles as potential inhibitors of the enzyme dihydrofolate reductase (DHFR) via this synthetic strategy.[3−9] An empirical rule has emerged from our studies as well as those of others,[10−12] which dictates that in annulation reactions involving substituted 6-aminopyrimidines (which have multiple competing sites for potential ring-annulation) and biselectrophiles such as β-keto aldehydes, β-keto esters, and β-dialdehydes as well as α-halo ketones, the 5-position of the pyrimidine is the most nucleophilic and attacks the most electrophilic carbon of the biselectrophile, followed by ring closure between the 6-amino group and the second electrophilic center. This experimental observation is supported by computational studies using AM1 and PM3 calculations, which reveal a direct correlation between charge densities at the C5-carbon of the above-mentioned 6-aminopyrimidines and their enamine-like nucleophilicity toward enones.[13] During the course of our continued studies toward the synthesis of bicyclic and tricyclic antifolates via utilization of this methodology, we discovered an unexpected reaction pathway leading to the formation of several novel, interesting heterocycles, which is the subject of this note.

Trimetrexate (TMQ) is a recently approved drug for the treatment of opportunistic infections in patients with acquired immunodeficiency syndrome (AIDS).[14] As part of a project aimed at synthesizing conformationally restricted analogues of TMQ, the tricyclic analogue **5** was sought, the seemingly trivial synthesis of which was initially attempted via the reaction of 2,4,6-triaminopyrimidine (**1**) with ethyl 2-cyclohexanonecarboxylate (**2**) in glacial acetic acid (Scheme 1). The expected mode of reactivity involves nucleophilic attack by the C5-carbon of **1** at the ketone moiety of **2** followed by ring closure between the 6-amino moiety and the ethyl ester. Unexpectedly, this reaction afforded two products in a 1:1 ratio, none of which was **5**. On the basis of the ^{1}H NMR[5,15] and the ^{13}C NMR, the two compounds were identified as **3** and **4**, which could be easily distinguished from one another by the downfield shift of one of the 2-amino protons of **3** which participates in a hydrogen bond with the lactam carbonyl. The suggested pathway for the formation of **3** and **4** via route i and route ii, respectively, is depicted in Scheme 1, and involves ring-formation between the N1-nitrogen and the 6-amino moiety. When the same reaction was performed under thermal conditions (diphenyl ether at 190 °C), **5** was obtained as the sole product, as reported by Hitchings et al.[11] This influence of reaction conditions on product composition in the reaction of 6-aminopyrimidines with β-keto esters being a novel observation, warranted further investigation.

The reaction of **1** with a simple, acyclic keto ester, ethyl acetoacetate **6**, would be predicted to afford **9** if the "normal" reactivity mode were followed (Scheme 2). Refluxing a mixture of **1** and **6** in acetic acid afforded a mixture of **7** and **8**, with none of the anticipated product **9**. When the same reaction was performed in diphenyl ether at 190−200 °C (the conditions followed for the synthesis of **5**) or dioxane at 100−110 °C, the sole product obtained was **9**, with the diagnostic lactam NH resonating at 8.43 ppm and the absence of the H5 proton in the ^{1}H NMR. Thus, in acetic acid, the N1-nitrogen of **1** behaves as the nucleophilic partner in lieu of the C5-

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(1) (a) Taken in part from the dissertation submitted by A. V. to the Graduate School of Pharmaceutical Sciences, Duquesne University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1996. (b) Taken in part from the dissertation submitted by F. M. to the Graduate School of Pharmaceutical Sciences, Duquesne University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1995. (c) Taken in part from the thesis submitted by L. C. to the Graduate School of Pharmaceutical Sciences, Duquesne University, in partial fulfillment of the requirements for the degree of Master of Science, June 1995.

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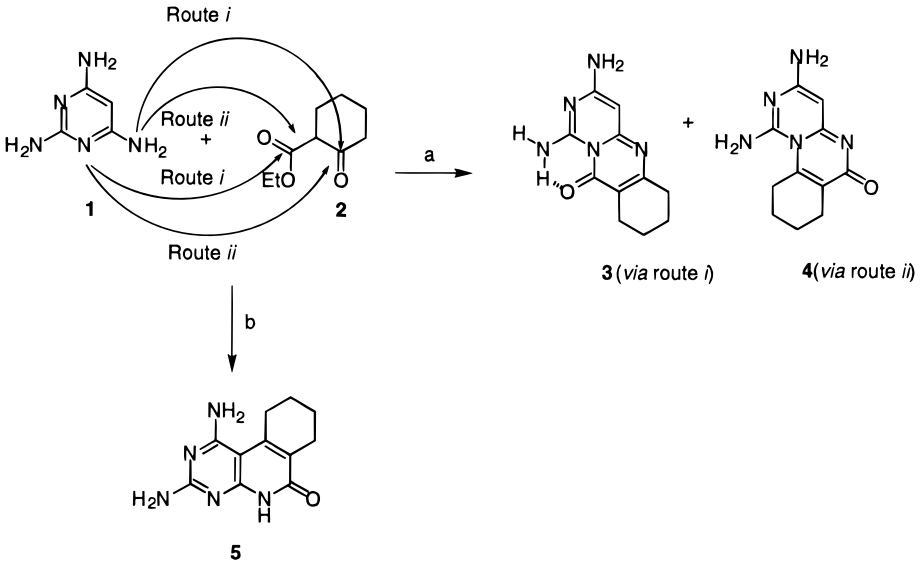
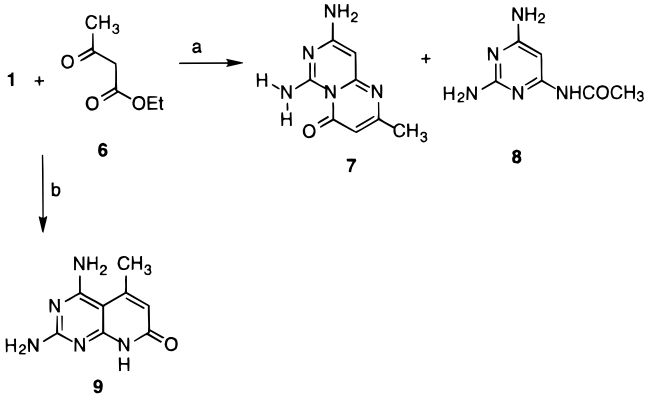
10.1021/jo9713870 CCC: $18.00
Published on Web 12/15/1998

Scheme 1[a]



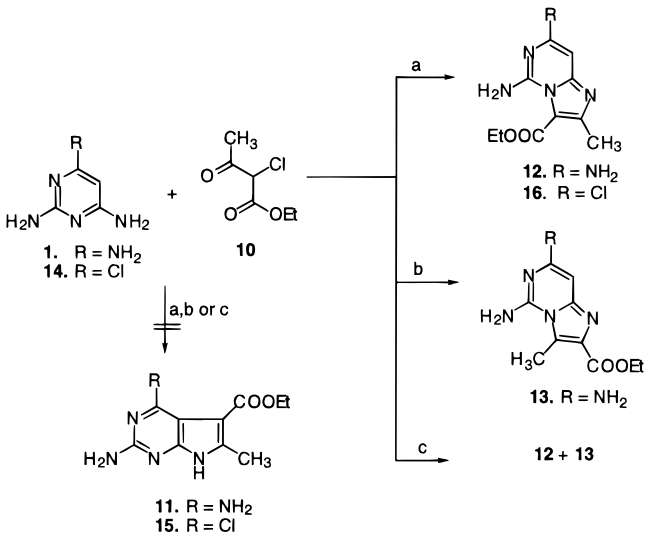
[a] Reaction conditions: (a) CH_3COOH, reflux 14 h; (b) diphenyl ether, 190 °C, 14 h.

Scheme 2[a]



[a] Reaction conditions: (a) CH_3COOH, reflux, 12 h; (b) diphenyl ether, 190−200 °C, 12 h.

Scheme 3[a]



[a] Reaction conditions: (a) NaOAc, H_2O, 60 °C, 1.5 h; (b) DMF, 50 °C, 12 h; (c) dioxane, reflux, 12 h.

carbon, in contrast to the speculation that reactions between β-dicarbonyl compounds and **1** (in acidic media) proceed via initial acylation of the C5-carbon followed by ring closure.[10] These results taken together with the observation that in reactions with **1**, introduction of substituents such as a methyl or phenyl group on **2**[16] or the use of a heterocyclic (piperidone or pyrrolidone) β-keto ester[17,18] afford tricyclics resulting from the participation of the C5-carbon and the 6-amino group in both acetic acid and diphenyl ether suggest that depending on the substitution the reactivity of **1** with β-keto esters in different solvents could be varied to afford products cyclized either at the N1-nitrogen or the C5-carbon.

To further investigate the participation by the N1-nitrogen of 6-aminopyrimidines in cyclizations with bi-selectrophiles other than keto esters, α-halo carbonyls were employed. Cyclocondensation of α-chloro carbonyls with 4-hydroxy-6-aminopyrimidines in DMF or NaOAc/H_2O have been reported[12,19−22] to yield pyrrolo[2,3-*d*]-pyrimidines and/or furo[2,3-*d*]pyrimidines, resulting from reaction between the C5-carbon and the 6-amino or 4-hydroxy group, respectively, with the biselectrophile. However, to our knowledge, the literature does not contain information regarding the cyclocondensation of unsubstituted 2,4,6-triaminopyrimidines with α-chloro carbonyl compounds. Reaction of **1** with **10** in solvents typically used in such reactions,[12,19−22] did not yield the pyrrolo[2,3-*d*]pyrimidine **11**, but rather imidazo[1,2-*c*]-pyrimidines **12** or **13** (Scheme 3). When a mixture of **1** and **10** was heated in sodium acetate/water, **12** was obtained exclusively. This corroborates literature re-

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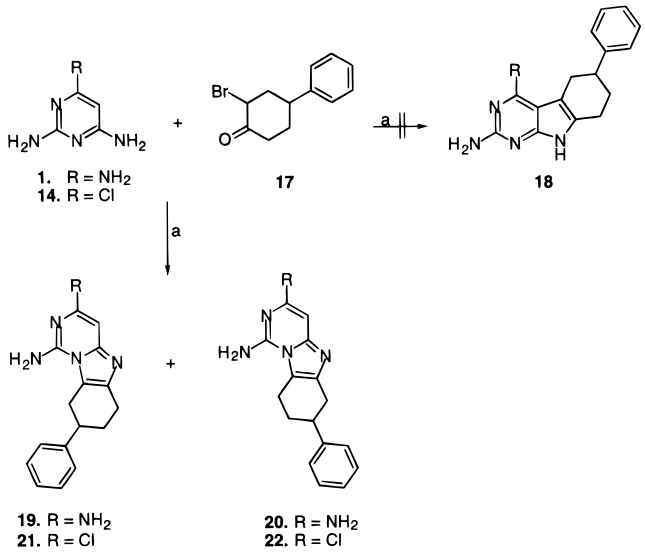
ports[12] that when aminopyrimidines annulate to form imidazopyrimidines, the exocyclic amino group bonds to the ketone of the α-halo carbonyl and the ring nitrogen to the halogen-containing carbon, perhaps on account of the intermolecular hydrogen bonding between the 6-amino moiety and water, as a result of which the N1-nitrogen reacts with the more reactive halogen-containing carbon. However, performing the same reaction in DMF where such strong intermolecular hydrogen bonding with the solvent should be disrupted, **13** is formed regiospecifically. Further, when **1** and **10** were refluxed in a solvent of lower polarity and solvation ability than water and DMF such as dioxane[23] for 12 h, no regiospecificity was observed, and a 1:1 mixture of **12** and **13** was obtained. None of the reaction conditions afforded the pyrrolo[2,3-*d*]pyrimidine **11**. Roth[24] has reported the formation of a thiazolo[3,2-*c*]pyrimidine as its sulfate via a similar N1-cyclization in the reaction of 2,4-diamino-6-mercaptopyrimidine with an α-halo ketone in sulfuric acid. While the possibility exists for the formation of **12** via the initial formation of **13** followed by a Dimroth-type rearrangement,[25] the conditions required for such a rearrangement (NaOH, reflux) are much too harsh compared to those utilized in this study. Reaction of **10** with 2,6-diamino-4-hydroxypyrimidine, which possesses an electron-withdrawing group at the 4(6)-position in DMF[12] or NaOAc−H_2O (data not shown) has been shown to afford a mixture of a pyrrolo[2,3-*d*]pyrimidine and furo[2,3-*d*]pyrimidine, suggesting that similar pyrimidines with electron-withdrawing groups at the 4-position might possess the requisite electron density at the C5-carbon to facilitate cyclization to occur at the 5-position, in either DMF or NaOAc−H_2O. Surprisingly, the cyclocondensation of 2,6-diamino-4-chloropyrimidine **14** with **10** in NaOAc−H_2O did not afford the desired pyrrolo[2,3-*d*]pyrimidine, but instead gave the N1 cyclized compound **16** (Scheme 3). No evidence for the presence any other regioisomer was detected.

To investigate the possible role of steric hindrance imposed by a phenyl substitution on the α-halo ketone on the direction of ring closure, the cyclocondensation of **1** and 2-bromo-4-phenylcyclohexanone **17** (obtained via bromination of 4-phenylcyclohexanone) was performed. Stirring **17** with **1** in DMF at 60 °C for 12 h afforded two regioisomeric imidazo[1,2-*c*]pyrimidines **19** and **20** as an inseparable mixture in a 2:3 ratio (Scheme 4), as determined by their ^{1}H NMR. These results are especially intriguing considering that the reaction of 2,4,6-triamino-substituted pyrimidine with α-bromocyclohexanone affords the product resulting from the condensation of the C5-carbon and the 6-amino moiety with the α-halo ketone.[26] This observation clearly suggests that steric factors play a role in determining the direction of ring closure in the reaction of α-halo carbonyls with triaminopyrimidines. The reaction of **14** with 2-bromo-4-phenylcyclohexanone **17** in DMF at 60 °C for 2 days resulted in the formation of one of the two possible imidazo[1,2-*c*]-

Scheme 4[a]



[a] Reaction conditions: (a) DMF, rt, 24 h.

pyrimidines **21** or **22**. (Scheme 4). No attempts were made to identify the precise regiochemistry of the cyclization.

To our knowledge, this is the first report where reaction of β-keto esters with **1** affords different regioisomers depending on acidic or thermal modes of cyclization. Robins and Hitchings,[10] in their pioneering work on the synthesis of pyrido[2,3-*d*]pyrimidines via the reaction of 6-aminopyrimidines with β-dicarbonyl compounds, did consider the possibility that N1-cyclized products could indeed occur in such reactions. However, in all cases reported by these workers, exclusive participation by the 5-position (in phosphoric acid) was observed, to afford regiospecifically pyrido[2,3-*d*]pyrimidines. N1-Cyclizations observed by Edstrom et al.[27] when 6-[(carboxymethyl)amino]pyrimidines were heated with acetic anhydride were *intra*molecular cyclizations, where the reactive electrophile was tethered to the pyrimidine ring via the 6-amino moiety, which benefits from the entropic advantage associated in constraining two reaction partners. The most basic nitrogen in **1** is N1, and its pK_a is 6.72,[28] implying that in acetic acid (pH = 4−5), the N1-nitrogen should be protonated, perhaps accounting for the reaction of the 6-amino moiety with the more reactive ketone carbonyl of **2**; however, subsequent ring closure via participation of the N1-nitrogen (to afford **3**) as opposed to the C5-carbon is unprecedented. Conversely, initial nucleophilic attack by the N1-nitrogen of the nonprotonated form of **1** on the ketone moiety of **2** followed by ring closure may account for the formation of **4**. The prediction that the nature of the product composition is most probably a combination of all three variables, namely the pyrimidine substitution and the solvent as well as the biselectrophile employed, is borne out by the fact that the presence of substitutents on the cyclic keto ester **2** such as a methyl or a phenyl moiety[16] or the use of a heterocyclic keto ester, such as a pyrrolidone[17] or piperidone keto ester,[18] promotes the cyclization to occur in acetic acid or phosphoric acid or diphenyl ether

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in the normal, anticipated manner, away from the N1-nitrogen, and at the C5-position. This unequivocally indicates that both steric as well as electronic effects operate in dictating the direction of ring closure. Previous studies[12] have suggested that a certain critical electron density (or HOMO coefficient) is necessary to facilitate reaction at the C5-carbon. The results obtained in this study conclusively indicate that not only is the electron density at the C5-carbon important, but the solvents utilized as well as the substitutions on the biselectrophile control the regiochemistry of the pyrimidine-annulated products. While it is reasonable to assume that the nucleophiliity of the C5-carbon in 2,6-diamino-4-hydroxypyrimidine and **14** are attenuated compared to **1** on account of the electron-withdrawing nature of the substitutent at the 4-position, participation by the N1-nitrogen in similar cyclizations, has not been reported. Further studies are underway to explore the application of this observed phenomenon in the synthesis of novel heterocycles and will be the subject of future communications.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus or a Mel Temp apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Brucker WH-300 (300 MHz). Low resolution mass spectra were obtained on an LKB-9000 instrument. Thin-layer chromatography was performed on silica gel plates with fluorescent indicator and were visualized with light at 254 and 366 nm, unless indicated otherwise. Column chromatography was performed with 230−400 mesh silica gel purchased from Aldrich Chemical Co., Milwaukee, WI. Elution was performed using a gradient, and 10 mL fractions were collected, unless mentioned otherwise. All anhydrous solvents were purchased from Aldrich Chemical Co. and were used without further purification. Samples for microanalysis were dried in vacuo over phosphorus pentoxide at 70 °C or 110 °C. Microanalysis were performed by Atlantic Microlabs, Norcoss, GA. All samples for elemental analyses were dried for 24−48 h, in vacuo at 110 °C. Traces of solvents present in the analytical data could not be removed and were confirmed, where possible, by their presence in the NMR spectra.

N1-Cyclization of 2,4,6-Triaminopyrimidine with Ethyl 2-Cyclohexanonecarboxylate. To a solution of 2,4,6-triaminopyrimidine **1** (1.0 g, 8.0 mmol) in glacial acetic acid was added ethyl 2-cyclohexanonecarboxylate **2** (1.36 g, 8.0 mmol) and the mixture refluxed for 14 h. TLC ($CHCl_3$:CH_3OH:NH_4OH 4:1:0.5) indicated the presence of two new products (R_f = 0.62 and 0.46) along with some unreacted triaminopyrimidine. The acetic acid was evaporated and the residue basified to pH 8 with NH_4OH. The solid obtained was collected by filtration, washed with hexanes, and dissolved in methanol with heating (50 °C). A 1.0 g amount of silica gel was added to the solution and the solvent evaporated to afford a dry plug. This plug was chromatographed on a 1.05 in. × 23 in. silica gel column using $CHCl_3$:CH_3OH 10:1 as the eluant. Fractions containing pure product were pooled and evaporated to afford **3** and **4** in a 1:1 ratio.

1,3-Diamino-5,6,7,8-tetrahydro[2,9-*a*]10-triazaanthracen-9-one (3). Appearance: cream solid, 0.57 g, 31%. TLC [$CHCl_3$:CH_3OH (4:1) R_f = 0.62]. mp = 251−254 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.62 (br s, 4 H), 2.25 (br s, 2 H), 2.37 (br s, 2 H), 5.36 (s, 1 H), 6.74 (br s, 2 H), 7.96 (br s, 1 H), 9.93 (br s, 1 H). ^{13}C NMR (DMSO-d_6, 75 MHz) 21.1, 22.0, 31.3, 81.0, 105.6, 152.5, 153.0, 158.0, 159.9, 162.1, 172.1. Anal. Calcd for $C_{11}H_{13}N_5O$·0.2 H_2O: C, 56.26; H, 5.75; N, 29.82. Found: C, 56.40; H, 5.40; N, 29.81.

2,4-Diamino-5,6,7,8-tetrahydro[3,4-*a*]10-triazaphenanthren-9-one (4). Appearance: cream solid, 0.55 g, 30%. TLC [$CHCl_3$:CH_3OH (4:1) R_f = 0.46]. mp = 231−234 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) 1.63 (br s, 4 H), 2.26 (br s, 2 H), 2.37 (br s, 2 H), 5.23 (s, 1 H), 5.86 (br s, 2 H), 8.62 (br s, 2 H). ^{13}C NMR-(DMSO-d_6, 75 MHz) 21.5, 22.1, 31.9, 77.7, 106.8, 151.0, 155.7, 161.6, 163.5, 164.4, 172.7. Anal. Calcd for $C_{11}H_{13}N_5O$·0.7H_2O: C, 54.18; H, 5.95; N, 28.72. Found: C, 53.81; H, 5.58; N, 28.37.

1,3-Diamino-7,8,9,10-tetrahydro-5*H*-pyrimido[4,5-*c*]isoquinolin-6-one (5). To a suspension of **1** (1.0 g, 8.0 mmol) in diphenyl ether at 190 °C in a three-necked flask fitted with a Dean−Stark trap was added ethyl 2-cyclohexanonecarboxylate (1.63 g, 9.6 mmol) and the mixture heated for 14 h. At the end of this period, the mixture was cooled and 100 mL of methanol added. The mixture was filtered and the residue on the funnel washed repeatedly with warm methanol to remove unreacted starting materials to afford 0.59 g (32%) of **5**. Appearance: brownish solid. mp > 300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.54 (br m, 4 H), 2.34 (br m, 2 H), 2.88 (br m, 2 H), 6.28 (br s, 2 H), 6.42 (br s, 2 H), 8.27 (br s, 1 H). Anal. Calcd $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.14; H, 5.30; N, 30.08.

N1-Cyclization of 2,4,6-Triaminopyrimidine with Ethyl Acetoacetate. 2,4,6-Triaminopyrimidine **1** (1.00 g, 8 mmol) was dissolved in 40 mL of glacial acetic acid, and ethyl acetoacetate **6** (1.04 g, 8 mmol) was added. The solution was refluxed for 12 h. TLC analyses ($CHCl_3$:CH_3OH:NH_4OH 5:1:0.5) indicated the presence of two new products (R_f = 0.34, 0.51) along with some unreacted **1**. The acetic acid was evaporated to afford a black, gummy residue, which was suspended in water and neutralized with 1 N Na_2CO_3, and the residue was filtered. The solid was then dissolved in a large amount (~ 100 mL) of methanol, 1.0 g silica gel added, and the methanol evaporated to afford a dry plug. This plug was applied on the surface of a silica gel column (1.05 in. × 23 in.) and eluted with $CHCl_3$:CH_3OH (5:1), and individual fractions were collected to afford **7** and **8** in a 1:1 ratio.

6,8-Diamino-4-methylpyrimido[1,6-*a*]pyrimidin-2-one (7). Appearance: white solid, 0.44 g, 29%. mp = 240−244 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.05 (s, 3 H), 5.43 (overlapping s, 2 H), 6.84 (br s, 2 H), 7.95 (s, 1 H), 9.96 (s, 1 H). Anal. Calcd for $C_8H_9N_5O$·0.9H_2O: C, 46.33; H, 5.25; N, 33.77. Found: C, 46.05; H, 5.13; N, 33.41.

***N*-Acetyltriaminopyrimidine (8).** Appearance: cream solid, 0.41 g, 31%. mp = 200−204 °C (softens). ^{1}H NMR (DMSO-d_6) δ 2.00 (s, 3 H), 5.29 (s, 2 H), 6.15 (s, 2 H), 6.50 (s, 1 H), 9.73 (s, 1 H). Anal. Calcd for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.89. Found: C, 43.02; H, 5.33; N, 41.53.

2,4-Diamino-5-methylpyrido[2,3-*d*]pyrimidin-7-one (9). 2,4,6-Triaminopyrimidine **1** (1.00 g, 8.00 mmol) was suspended in 50 mL of diphenyl ether and ethyl acetoacetate (1.04 g, 8.00 mmol) added. The mixture was heated at 190−200 °C for 12 h in a three-neck flask equipped with a Dean−Stark trap to facilitate continuous removal of water and ethanol. TLC analyses ($CHCl_3$:CH_3OH 5:1) at the end of 12 h indicated the presence of a new product. The reaction mixture was cooled to room temperature and the residue collected by filtration. It was then dissolved in 250 mL of boiling methanol, 1.0 g silica gel was added, and the solvent was evaporated to afford a dry plug. Chromatography of the plug on a 1.05 in. × 23 in. silica gel column afforded **9** (0.78 g, 51%). mp > 300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.45 (s, 3 H), 5.23 (s, 1 H), 6.45 (br s, 2 H), 6.98 (s, 2 H), 8.91 (s, 1 H). Anal. Calcd for $C_8H_9N_5O$·0.3H_2O: C, 48.88; H, 4.92; N, 35.62. Found: C, 48.57; H, 4.61; N, 35.24.

Reaction of 2,4,6-Triaminopyrimidine with Ethyl 2-Chloroacetoacetate. 2,4,6-Triaminopyrimidine (1.00 g, 8.00 mmol) was heated in dioxane at 100 °C. At this temperature, ethyl 2-chloroacetoacetate was added and the reaction mixture heated at 100 °C for 24 h. The mixture was cooled to room temperature and filtered and the filtrate washed with 100 mL of methanol. Separation of the two components via silica gel chromatography afforded two analytically pure products which were similar in all respects to those obtained via the alternate conditions described below for the synthesis of **12** and **13**.

5,7-Diamino-2-methylimidazo[1,2-*c*]pyrimidine-3-carboxylic Acid Ethyl Ester (12). A solution of 2,4,6-triaminopyrimidine **1** (1.26 g, 10.0 mmol) in water (15 mL) containing NaOAc (0.80 g, 9.70 mmol) was heated to 60 °C. Ethyl 2-chloroacetoacetate **10** (1.37 mL, 10.0 mmol) was added to this warm solution, and the reaction mixture was heated at 60 °C for an additional 90 min after which it was cooled to room temperature and filtered. The residue was dissolved in 25 mL of MeOH and filtered and the filtrate evaporated to dryness to yield 0.64 g (27%) of **12** as a yellow solid: MS *m*/*z* 235 (M^+); TLC R_f 0.75 ($CHCl_3$/MeOH 9:4, silica gel), 0.49 ($CHCl_3$/EtAc/MeOH, 5:1:1,

silica gel); mp = 236−240 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.28 (t, 3H), 2.42 (s, 3H), 4.25 (q, 2H), 5.64 (s, 1H), 6.22 (s, 2H), 8.23 (bs, 2H). Anal. Calcd for $C_{10}H_{13}N_5O_2 \cdot 1.5H_2O$: C, 45.80; H, 6.15; N, 26.70. Found: C, 45.49; H, 5.76; N, 27.09.

5,7-Diamino-3-methylimidazo[1,2-*c*]pyrimidine-2-carboxylic Acid Ethyl Ester (13). A mixture of 2,4,6-triaminopyrimidine **1** (1.26 g, 10.0 mmol) and ethyl 2-chloro acetoacetate **10** (1.37 mL, 10.0 mmol) in DMF (15 mL) was stirred at 50 °C for 26 h. The reaction mixture was cooled to room temperature, and the resulting suspension was filtered and washed with DMF. The residue was dissolved in hot MeOH (50 mL) and filtered. The filtrate was refrigerated and the resulting precipitate filtered, washed with acetone, and dried under vacuum over P_2O_5 to yield 0.58 g (23%) of **13** as a buff solid: TLC R_f 0.2 ($CHCl_3$/EtAc/MeOH 5:1:1, silica gel), mp = 201−203 °C, ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33 (t, 3H), 2.48 (s, 3H), 4.30 (q, 2H), 5.54 (s, 1H), 7.01 (s, 2H), 8.28 (s, 2H). Anal. Calcd for $C_{10}H_{13}N_5O_2 \cdot 0.5H_2O$: C, 49.17; H, 5.78; N, 28.67. Found: C, 48.78; H, 5.40; N, 29.06.

5-Amino-7-chloro-2-methylimidazo[1,2-*c*]pyrimidine-3-carboxylic Acid Ethyl Ester (16). To a solution of 2,6-diamino-4-chloropyrimidine **14** (1.44 g, 10.0 mmol) in water (30 mL) containing NaOAc (0.60 g, 7.30 mmol) and heated to 100 °C was added ethyl 2-chloroacetoacetate **10** (1.37 mL, 10.0 mmol). After heating at 100 °C for 5 h the reaction was complete. It was then cooled to room temperature, filtered, and washed with hot water. The residue was dissolved in 25 mL of MeOH and filtered, and the filtrate was concentrated to yield 0.38 g (15%) of **16** as white, crystalline needles: mp >160 °C; TLC R_f 0.76 ($CHCl_3$/MeOH/NH_4OH 9:4:0.1, silica gel); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.35 (t, 3H), 2.66 (s, 3H), 4.35 (q, 2H), 6.89 (s, 1H), 8.89 (bs, 2H); ^{1}H NMR (TFA-*d*, 300 MHz) δ 1.39 (t, 3H), 2.71 (s, 3H), 4.49 (q, 2H), 6.96 (s, 1H). Anal. Calcd for $C_{10}H_{11}N_4O_2Cl$: C, 47.16; H, 4.35; N, 22.00; Cl, 13.92. Found: C, 47.22; H, 4.36; N, 22.02; Cl, 13.95.

Reaction between 2,4,6-Triaminopyrimidine and 2-Bromo-4-phenylcyclohexanone (19, 20). A mixture of 2,4,6-triaminopyrimidine **1** (0.25 g, 1.98 mmol) and 2-bromo-4-phenylcyclohexanone **17** (0.50 g, 1.98 mmol) in DMF (12 mL) was stirred at room-temperature overnight. The resulting solution was concentrated under reduced pressure, and the residue was purified on a silica gel column with gradient 10%, 12.5%, 15%, and 17.5% of MeOH/CH_2Cl_2. The fractions with R_f = 0.5 (20% MeOH/ CH_2Cl_2) were pooled and concentrated to give two products (**19** and **20**) (0.25 g, 46%) in a 2:3 ratio, as determined by ^{1}H NMR.

1,3-Diamino-8-phenyl-6,7,8,9-tetrahydrobenzo[4,5]-imidazo[1,2-*c*]pyrimidine (19) and 1,3-Diamino-7-phenyl-6,7,8,9-tetrahydrobenzo[4,5]imidazo[1,2-*c*]pyrimidine (20). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.37−7.30 (m, 5H), 7.21−6.70 (br m, 4H, exchanges with D_2O), 5.70 (s, 2/5 H), 5.54 (s, 3/5 H), 3.32−2.65 (m, 5H), 2.00 (m, 2H). HRMS calcd for $C_{16}H_{17}N_5$ 279.1484, found 279.1434.

3-Chloro-7(or 8)-phenyl-6,7,8,9-tetrahydrobenzo[4,5]-imidazo[1,2-*c*]-pyrimid-1-ylamine, 21 (22). A mixture of 4-chloro-2,6-diaminopyrimidine **14** (0.71 g, 4.91 mmol) and 2-bromo-4-phenylcyclohexanone **17** (1.24 g, 4.90 mmol) in DMF (12 mL) was heated to 60 °C for 3 days. The resulting precipitate was collected by filtration to give the product as an off-white solid (0.47 g, 32%): ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.34 (br s, 2H), 7.39−7.12 (m, 5H), 6.47 (s, 1H), 3.48−3.10 (m, 3H), 2.82 (m, 2H), 2.09−2.02 (m, 2H). HRMS calcd for $C_{16}H_{15}ClN_4$ 298.0985, found 298.0983.

Acknowledgment. This work was supported in part by grants from the NIH, National Institute of General Medical Sciences (GM40998), and the National Institute of Allergy and Infectious Diseases (AI41743). We would like to thank Dr. Fu-Tyan Lin (University of Pittsburgh) for the ^{13}C NMR spectra.

JO9713870