An Improved Synthesis of 7-Substituted Pyrrolo[3,2-*d*]pyrimidines

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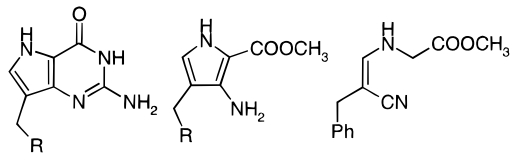
Base (NaOMe)-catalyzed condensation of 3,3-dimethoxypropionitrile with aldehydes followed by hydrolysis with 6 N HCl gives the unsaturated cyano aldehydes **5**. Catalytic reduction of the double bond followed by reaction with diethyl aminomalonate affords the enamines **7**, which cyclize to the aminopyrroles **2** on treatment with NaOMe. While the amino group in **2** is unreactive toward many guanylating reagents, acid (AcOH)-catalyzed guanylation occurs easily with **10** to give **12** along with methyl mercaptan as a byproduct. Subsequent facile removal of the carbamate groups and ring closure to the pyrrolo[3,2-*d*]pyrimidine ring system occurs on treatment with base. The use of $HgCl_2$ in place of AcOH ties up the mercaptan and eliminates the odor problem. For larger scale reactions where the mercaptan odor and the use of Hg salts are undesirable, the use of the methoxy analogue **11** is preferred. Using this procedure, benzaldehyde has been converted to the 7-(phenylmethyl)pyrrolo[3,2-*d*]pyrimidine **(1a)**, a potent inhibitor of the enzyme purine nucleoside phosphorylase, in 31% overall yield with only three isolation steps.

Purine nucleoside phosphorylase (PNP) is a salvage enzyme important to the T-cell-mediated part of the immune system and, as such, is an important therapeutic target. Our group has described the synthesis and potent PNP inhibitory activity of a series of 7-substituted 2-amino-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-ones **1**,[1−4] and the 3-(pyridinylmethyl) derivative (BCX-34, USAN peldesine) is in clinical trials for the treatment of T-cell cancers, psoriasis, and AIDS. As part of our analogue preparation and process development activities, we required an improved synthesis of compounds of general structure **1**, and the results of some of our studies are reported in this paper.



1 **2** **3**

a: R = phenyl
b: R = 1-naphthyl
c: R = 2-naphthyl
d: R = 4-biphenyl
e: R = 4-isopropylphenyl
f: R = 4-trifluoromethylphenyl
g: R = cyclohexyl
h: R = 2-furanyl
i: R = 3-thienyl

For convenience, we initially focused on the 7-(phenylmethyl) derivative **1a** to develop our synthetic route. The literature procedure[1] to **1a** employed, as a key intermediate, the pyrrole **2a**, which was made by base (DBN)-catalyzed cyclization of the enamine **3**. A protection/deprotection sequence of the *NH* of **3** as a carbamate derivative was necessary in order for the cyclization to proceed, and column chromatography was required to separate the product **2a** from the DBN. Since we had previously shown[5] that the use of diethyl aminomalonate in place of methyl glycinate allows similar cyclizations to proceed without the need for *NH* protection, we decided to study the cyclization of enamine **7a**.

Our eventual route to **7a** is shown in Scheme 1. While the reported[1] base-catalyzed formylation of hydrocinnamonitrile to give **6a** worked well in our hands, the nitriles necessary for many of the compounds we intended to prepare are not available commercially. Since the aldehydes are more readily available, these were chosen as suitable starting materials. NaOMe-catalyzed condensation of benzaldehyde with 3,3-dimethoxypropionitrile gave **4a** as an oil that was converted to the crystalline unsaturated aldehyde **5a** in 6 N HCl. The relative stereochemistry around the double bond was not determined. While initially **4a** was purified and characterized, it was found to be more convenient to remove the methanol and treat the crude reaction mixture with 6 N HCl directly. In this way, **5a** could be obtained in 74% yield from benzaldehyde. Compound **5a** has previously been reported, without characterization, by the base-catalyzed condensation of benzaldehyde and 3-oxopropanenitrile, generated in situ from isoxazole.[11] Our route was found to be an extremely facile way of producing unsaturated aldehydes **5b**−**i** from a variety of substituted benzaldehydes as well as heteroaromatic and alicyclic aldehydes. This route did not work well with aryl alkyl ketones, however, since, under basic reaction conditions, self-condensation tended to be the predominant condensation reaction.

Catalytic hydrogenation of **5a** in MeOH followed by condensation of the resulting **6a** with diethyl aminoma-

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(1) Montgomery, J. A.; Niwas, S.; Rose, J. D.; Secrist, J. A., III; Babu, Y. S.; Bugg, C. E.; Erion, M. D.; Guida, W. C.; Ealick, S. E. *J. Med. Chem.* **1993**, *36*, 55−69.

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(3) Erion, M. D.; Niwas, S.; Rose, J. D.; Ananthan, S.; Allen, M.; Secrist, J. A., III; Babu, Y. S.; Bugg, C. E.; Guida, W. C.; Ealick, S. E.; Montgomery, J. A. *J. Med. Chem.* **1993**, *36*, 3771−3783.

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(7) Yamazaki, A.; Okutsu, M. *J. Heterocycl. Chem.* **1978**, *15*, 353−358.

(8) Lewis, A. F.; Townsend, L. B. *J. Am. Chem. Soc.* **1982**, *104*, 1073−1077.

(9) Skibinski, A.; Stec, Z.; Januchowski, M.; Parys, L. Pol. *J. Appl. Chem.* **1993**, *37*, 291−294.

(10) Viswananthan, N. Indian Patent 168,784; *Chem. Abstr.* **1993**, *118*, 22237.

(11) Ciller, J. A.; Martin, N.; Seoane, C.; Soto, J. L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2581−2584.

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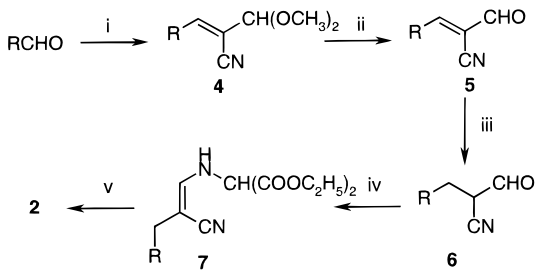
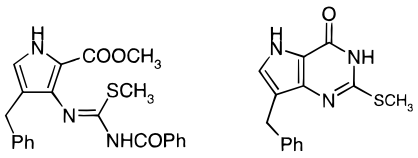
Scheme 1[a]



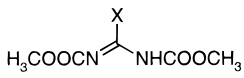
[a] Key: (i) $NCCH_2CH(OCH_3)_2$, NaOMe; (ii) 6 N HCl; (iii) H_2, Pd/C; (iv) $H_2NCH(COOEt)_2$; (v) NaOMe, MeOH.

lonate gave the required enamine **7a**. On treatment with NaOMe in MeOH at room temperature, **7a** was smoothly converted to **2a**. Removal of the MeOH and addition of water gave essentially pure pyrrole **(2a)** in 57% yield, and thus, this sequence obviated the need for purification by column chromatography. Other pyrroles **(2b−i)** behaved similarly.

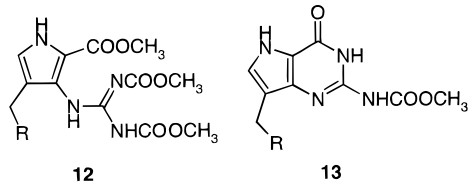
With an efficient synthesis of the key pyrrole in hand, we turned our attention to its conversion to the pyrrolo[3,2-*d*]pyrimidine ring system. The obvious and most direct route for the construction of the 2-aminopyrimidine ring would be the condensation of **2a** with guanidine salts, cyanamide, or *S*-methylisothiourea. However, the NH_2 group in **2a** and other pyrroles proved to be unreactive toward these reagents. The literature[1,6−8] procedure employed a circuitous route in which benzoyl isothiocyanate was reacted with **2a** to afford the *N*-benzoyl(thiocarbamoyl) derivative which was *S*-methylated with methyl iodide in the presence of DBN to give **8**. Reaction of **8** with methanolic ammonia in a pressure vessel at ca. 100 °C gave **1a** in ca. 50% yield but was contaminated with the 2-methylthio derivative **9**. This route was not attractive because of the high cost of benzoyl isothiocyanate and DBN, the toxicity of methyl iodide, the use of a pressure vessel, the formation of the byproduct **9**, and the release of methyl mercaptan.



We initially examined the more reactive 1,3-dicarbomethoxy-2-methyl-2-thiopseudourea[9] **10** as the guanylating agent. While all attempts at thermal condensation reactions were unsuccessful, condensation of **10** with **2a** proved facile using mercury catalysis giving **12a** in 75% yield. However, this method was not deemed suitable for pharmaceutical preparations of these compounds since the removal of the mercury salts to acceptable ppm levels is difficult. The condensation also went smoothly under mild acid catalysis, and the use of 5 equiv of AcOH in MeOH was found to be efficient in producing **12a** and related adducts. While **12a** could be isolated,



10: X=SCH_3
11: X=OCH_3



it was usually more convenient to add an excess of NaOMe, whereupon **12a** underwent cyclization and loss of one carbamate group to give **13a** in 70% overall yield. While the use of AcOH catalysis was an improvement, the methyl mercaptan produced during the reaction was not now complexed with the mercury and the mercaptan odor became a problem during large-scale preparations. This problem was obviated by the use of the methoxy analogue **11**,[10] which also condensed with **2a** under AcOH catalysis in MeOH. In this case, in situ cyclization of the adduct **12a** gave **13a** in 76% overall yield. The remaining carbamate group was then removed using aqueous NaOH at 55 °C to give **1a** in 97% yield. Compounds **1b−i** were prepared similarly.

While the use of **11** as the guanylating agent was preferred on a large scale, the use of **10** does have some merit for laboratory preparations since it is more stable, and for sluggish reactions, heating or mercury catalysis can be employed. When **11** is allowed to stand at room temperature for extended periods or solutions are heated, loss of one carbamate group tends to occur, and the resulting monocarbamate does not undergo guanylation reactions with **2a**.

In summary, we have developed an efficient new procedure for the production of 7-substituted pyrrolo[3,2-*d*]pyrimidines that is amenable to scale-up. As an example, **1a** may be obtained in 31% overall yield from benzaldehyde with only three isolation steps.

Experimental Section

General Methods. ^1H NMR spectra were recorded at 400 MHz unless otherwise stated, and the chemical shifts are reported relative to internal TMS. MS were obtained using a Fisons VG Trio 2000 mass spectrometer operating in the electrospray mode. IR were recorded on a Bio-Rad FTS-7 spectrophotometer. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Atlantic Microlab in Atlanta, GA, performed elemental analyses.

General Procedure for the Aldehydes 5. 2-(Dimethoxymethyl)-3-phenylacrylonitrile (4a). Benzaldehyde (79.5 g, 0.75 mol) and 3,3-dimethoxypropionitrile (115.1 g, 1.0 mol) were mixed together and added to a solution of NaOMe (54.0 g, 1.0 mol) in MeOH (400 mL) during 15 min. The mixture was stirred at room temperature overnight. Most of the MeOH was removed in vacuo, and the residue was partitioned between EtOAc (500 mL) and water (450 mL). The organic layer was separated, washed with brine (400 mL), and dried ($MgSO_4$) and the solvent evaporated in vacuo. The residual oil was distilled to give **4a** (103 g, 68%) as a colorless oil: bp 125−130 °C (2 mmHg); ^1H NMR ($CDCl_3$) δ 3.42 (s, 6H), 5.05 (s, 1H), 7.33 (s, 1H), 7.4−7.9 (m, 5H); IR (film) 2938, 2834, 2216, 1626 cm^{-1}; MS (ES^+) 172.1 ($MH^+ - CH_3OH$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.68; H, 6.50; N, 6.88.

2-Cyano-3-phenylpropenal (5a). From Pure 4a. HCl (6 N, 75 mL) and **4a** (5.0 g, 0.025 mol) and were stirred together at room temperature for 30 min. The colorless solid was collected by filtration, washed with water, and dried in air to give **5a** (3.9 g, 100%). A portion was crystallized from ether−hexane as colorless needles: mp 96−7 °C; ^1H NMR ($CDCl_3$) δ 7.5−7.7 (m, 3H), 7.92 (s, 1H), 8.0−8.1 (m, 2H), 9.61 (s, 1H); IR (KBr) 2223, 1692 cm^{-1}; MS (ES^+) 158.5 (MH^+). Anal. Calcd for $C_{10}H_7NO$: C, 76.42; H, 4.49; N, 8.91. Found: C,

76.17; H, 4.58; N, 8.83. **From Crude 4a.** Following the removal of MeOH in the preparation of **4a** above, the reaction mixture was treated cautiously with 6 N HCl (1.5 L), and the mixture was stirred at room temperature for 2 h. The solid was filtered off, washed well with water, and dried in vacuo to give **5a** (112.7 g, 74%) as an off-white solid, identical with the product obtained from pure **4a**.

In those cases where the product was not solid, the aldehyde was extracted with EtOAc, the extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give an oil that was used directly. An analytical sample was characterized as the 2,4-dinitrophenylhydrazone.

2-Cyano-3-(1-naphthyl)propenal (5b): 68% yield; yellow needles; mp 172−174 °C from toluene; ^{1}H NMR ($CDCl_3$) δ 7.6−8.5 (m, 7H), 8.83 (s, 1H), 9.77 (s, 1H); IR (KBr) 2221, 1691 cm^{-1}; MS (ES$^+$) 208.8 (MH$^+$). Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 80.87; H, 4.44; N, 6.74.

2-Cyano-3-(2-naphthyl)propenal (5c): 61% yield; yellow needles; mp 127−129 °C from toluene; ^{1}H NMR (DMSO-d_6) δ 7.6−8.3 (m, 6H), 8.57 (s, 1H), 8.65 (s, 1H), 9.69 (s, 1H); IR (KBr) 2221, 1693, 1600 cm^{-1}; MS (ES$^+$) 208.2 (MH$^+$). Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.22; H, 4.43; N, 6.73.

2-Cyano-3-(4-phenylphenyl)propenal (5d): 61% yield; yellow needles; mp 166−8 °C from toluene−hexane; ^{1}H NMR ($CDCl_3$) δ 7.4−8.2 (m, 9H), 7.93 (s, 1H), 9.61 (s, 1H); IR (KBr) 2224, 1688 cm^{-1}; MS (ES$^-$) 232.4 (M − H). Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.13; H, 4.80; N, 5.98.

2-Cyano-3-(4-isopropylphenyl)propenal (5e): 60% yield, characterized as the 2,4-dinitrophenylhydrazone; orange needles; mp 277−8 °C from MeOH; ^{1}H NMR (DMSO-d_6) δ 1.24 (d, J = 6.9 Hz, 6H), 2.97 (m, 1H), 7.4−8.4 (m, 7H), 8.54 (s, 1H), 8.80 (d, 1H), 11.9 (br s, NH); IR (KBr) 3432, 3283, 1620, 1594 cm^{-1}; MS (ES$^-$) 378.4 (M − H). Anal. Calcd for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46. Found: C, 60.01; H, 4.48; N, 18.46.

2-Cyano-3-[4-(trifluoromethyl)phenyl]propenal (5f): 23% yield, characterized as the 2,4-dinitrophenylhydrazone; orange needles; mp 278−80 °C from MeOH; ^{1}H NMR (DMSO-d_6) δ 7.9−8.6 (m, 7H), 8.65 (s, 1H), 8.86 (d, 1H), 11.9 (br s, NH); IR (KBr) 3295, 1618 1507, 1347, 1321 cm^{-1}; MS (ES$^-$) 404.4 (M − H). Anal. Calcd for $C_{11}H_6N_5O_4F_3$: C, 50.38; H, 2.49; N, 17.28. Found: C, 50.45; H, 2.52; N, 17.35.

2-Cyano-3-cyclohexylpropenal (5g): 76% yield, characterized as the 2,4-dinitrophenylhydrazone; orange needles; mp 228−30 °C from MeOH; ^{1}H NMR (DMSO-d_6) δ 1.1−2.7 (m, 11H), 6.8−8.9 (m, 4H), 8.39 (s, 1H), 11.7 (br s, NH); IR (KBr) 3294, 2945, 2855, 2234, 1619 cm^{-1}; MS (ES$^-$) 341.9 (M − H). Anal. Calcd for $C_{16}H_{17}N_5O_4$: C, 55.97; H, 4.99; N, 20.40. Found: C, 55.76; H, 4.98; N, 20.30.

2-Cyano-3-(2-furyl)propenal (5h): 67% yield; light orange needles; mp 156−8 °C from 2-propanol; ^{1}H NMR ($CDCl_3$) δ 6.7−8.0 (m, 3H), 7.73 (s, 1H), 9.52 (s, 1H); IR (KBr) 2225, 1680, 1616 cm^{-1}; MS (ES$^+$) 148.1 (MH$^+$). Anal. Calcd for $C_8H_5NO_2$: C, 65.30; H, 3.43; N, 9.52. Found: C, 65.24; H, 3.47; N, 9.53.

2-Cyano-3-(3-thienyl)propenal (5i): 69% yield; colorless needles; mp 123−4 °C from ether; ^{1}H NMR ($CDCl_3$) δ 7.5−8.3 (m, 3H), 7.96 (s, 1H), 9.57 (s, 1H); IR (KBr) 2225, 1680, 1616 cm^{-1}; MS (ES$^+$) 164.0 (MH$^+$). Anal. Calcd for C_8H_5NOS: C, 58.88; H, 3.09; N, 8.59. Found: C, 58.92; H, 3.09; N, 8.58.

General Procedure for the Pyrroles 2. Methyl 3-Amino-4-(phenylmethyl)-1*H*-pyrrole-2-carboxylate (2a). Compound **5a** (3.14 g, 0.02 mol), MeOH (100 mL), and 10% Pd/C (0.2 g) were shaken together under ca. 50 psig H_2 in a hydrogenation bottle for 35 min. The catalyst was removed by filtration, a mixture of diethyl aminomalonate (6.35 g, 0.03 mol), sodium acetate (2.46 g, 0.03 mol), and water (20 mL) was added, and the mixture was stirred at room temperature overnight. Most of the MeOH was removed in vacuo, and the residue was partitioned between EtOAc (250 mL) and water (200 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The residual yellow oil was dissolved in MeOH (100 mL) containing NaOMe (0.54 g, 0.01 mol), stirred at room temperature for 2 h and then boiled under reflux for 30 min. Most of the MeOH was evaporated in vacuo, and the residue was treated with water (200 mL) to give **2a** as a light yellow solid (1.3 g, 57%). An analytical sample was obtained from cyclohexane as off-white needles: mp 98−100 °C (lit.[1] mp 96−98 °C); ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 2H), 3.69 (s, 3H), 4.84 (br s, *NH*$_2$), 6.47 (d, 1H, J = 3.4 Hz), 7.2−7.3 (m, 5H), 10.48 (br s, *NH*); IR (KBr) 3388, 3312, 3148, 2916, 1683 cm^{-1}; MS (ES$^+$) 230.9 (MH$^+$). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.82; H, 6.16; N, 12.16.

The following pyrroles were obtained similarly. Where no crystallization solvent is given, the crude product was obtained analytically pure.

Methyl 3-amino-4-(1-naphthylmethyl)-1*H*-pyrrole-2-carboxylate (2b): 36% yield; cream solid; mp 128−9 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 4.14 (s, 2H), 4.3 (br s, *NH*$_2$), 6.4 (br s, 1H), 7.2−8.3 (m, 7H), 8.3 (br s, *NH*); IR (KBr) 3454, 3196, 1697, 1679 cm^{-1}; MS (ES$^+$) 281.1 (MH$^+$). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84; H, 5.79; N, 9.90.

Methyl 3-amino-4-(2-naphthylmethyl)-1*H*-pyrrole-2-carboxylate (2c): 74% yield; orange solid; mp 91−2 °C; ^{1}H NMR (DMSO-d_6) δ 3.69 (s, 3H), 3.81 (s, 2H), 4.88 (br s, *NH*$_2$), 6.53 (d, J = 3.3 Hz, 1H), 7.3−7.9 (m, 7H,), 10.52 (br s, *NH*); IR (KBr) 3407, 3328, 1687, 1672, 1598 cm^{-1}; MS (ES$^+$) 281.3 (MH$^+$). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.03; H, 5.80; N, 9.94.

Methyl 3-amino-4-[(4-phenylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (2d): 44% yield; light brown prisms; mp 162−4 °C from toluene; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 3.83 (s, 2H), 4.1 (br s, *NH*$_2$), 6.57 (br s, 1H), 7.2−7.7 (m, 9H,), 8.2 (br s, *NH*); IR (KBr) 3400, 3133, 2901, 1680 cm^{-1}; MS (ES$^+$) 307.3 (MH$^+$). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.36; H, 5.99; N, 9.14.

Methyl 3-amino-4-[(4-isopropylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (2e): 60% yield; light brown plates; mp 68−70 °C from cyclohexane; ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 6.9 Hz, 6H), 2.87 (m, 1H), 3.69 (s, 2H), 3.81 (s, 3H), 4.2 (br s, *NH*$_2$), 6.53 (br s, 1H), 7.14 (s, 4H), 8.2 (br s, *NH*); IR (KBr) 3412, 3332, 3181, 2961, 1686, 1672 cm^{-1}; MS (ES$^+$) 273.4 (MH$^+$). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.64; H, 7.36; N, 10.34.

Methyl 3-amino-4-[(4-(trifluoromethyl)phenyl]methyl]-1*H*-pyrrole-2-carboxylate (2f): 77% yield; off-white needles; mp 88−90 °C from cyclohexane; ^{1}H NMR ($CDCl_3$) δ 2.8 (br s, *NH*$_2$), 3.78 (s, 2H), 3.83 (s, 3H), 6.53 (br s, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 8.2 (br s, *NH*); IR (KBr) 3421, 3337, 3197, 1680, 1600 cm^{-1}; MS (ES$^+$) 299.4 (MH$^+$). Anal. Calcd for $C_{14}H_{13}N_2O_2F_3$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.76; H, 4.52; N, 9.10.

Methyl 3-amino-4-(cyclohexylmethyl)-1*H*-pyrrole-2-carboxylate (2g): 56% yield; colorless needles; mp 79−80 °C from hexane; ^{1}H NMR ($CDCl_3$) δ 0.8−1.9 (m, 11H), 2.23 (d, J = 7.0 Hz, 2H), 3.82 (s, 3H), 4.2 (br s, *NH*$_{2)}$, 6.53 (d, J = 3.2 Hz, 1H), 9.17 (br s, *NH*); IR (KBr) 3394, 3308, 3149, 2922, 2846, 1678 cm^{-1}; MS (ES$^+$) 236.9 (MH$^+$). Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.18; H, 8.61; N, 11.86.

Methyl 3-amino-4-(2-furylmethyl)-1*H*-pyrrole-2-carboxylate (2h): 22% yield; colorless plates; mp 126−8 °C (lit.[1] mp 133−4 °C) from toluene; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 3.82 (s, 3H), 4.3 (br s, *NH*$_2$), 6.0−7.5 (m, 3H), 6.62 (br s, 1H), 8.20 (br s, *NH*); IR (KBr) 3390, 3317, 3116, 2921, 1678 cm^{-1}; MS (ES$^+$) 221.4 (MH$^+$). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.99; H, 5.53; N, 12.78.

Methyl 3-amino-4-(3-thienylmethyl)-1*H*-pyrrole-2-carboxylate (2i): 34% yield; colorless needles; mp 108−110 °C (lit.[1] mp 108−9 °C) from toluene−cyclohexane; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 3.82 (s, 3H), 4.3 (br s, *NH*$_2$), 6.56 (br s, 1H), 6.9−7.3 (m, 3H), 8.10 (br s, *NH*); IR (KBr) 3390, 3312, 3143, 2921, 2914, 1681, 1606 cm^{-1}; MS (ES$^+$) 237.1 (MH$^+$). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.85. Found: C, 55.84; H, 5.20; N, 11.75.

General Method for the Adducts 12. Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-(phenylmethyl)-1*H*-pyrrole-2-carboxylate (12a). From 10 Using Mercury Catalysis. The pyrrole **2a** (4.6 g, 0.02 mol) was dissolved in DMF (35 mL) containing triethyl-

amine (7.1 g, 0.07 mol) and **10**[9] (4.5 g, 0.022 mol) at 4 °C. $HgCl_2$ (6.0 g, 0.022 mol) was added in one portion, and the mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the product was dissolved in EtOAc (200 mL) and filtered through a short silica gel plug to remove inorganics. The solvent was removed to give 5.8 g (75%) of **12a**. An analytical sample was obtained as colorless needles, mp 158−60 °C, by recrystallization from MeOH: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.80 (s, 3H), 3.83 (s, 5H), 6.44 (d, 1H, J = 4.21 Hz), 7.1−7.3 (m, 5H), 9.04 (br s, *NH*), 9.96 (br s, *NH*), 11.72 (br s, *NH*); IR (KBr) 3192, 1730, 1696, 1650, 1614 cm^{-1}; MS (ES$^+$) 389.3 (MH$^+$). Anal. Calcd for $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.74; H, 5.22; N, 14.53. **From 10 Using AcOH Catalysis.** The pyrrole **2a** (2.3 g, 0.01 mol) and **10** (2.27 g, 0.011 mol) were stirred together in MeOH (50 mL), and AcOH (3.0 g, 0.05 mol) was added. The mixture was stirred at room temperature overnight, and the precipitate was collected by filtration and recrystallized from 2-propanol to give **12a** (1.6 g, 41%) identical with the material obtained above. **From 11 Using AcOH Catalysis.** Using **11** in place of **10** above gave similar results.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-(1-naphthylmethyl)-1*H*-pyrrole-2-carboxylate (12b): 32% yield; colorless needles; mp 180−82 °C from 2-propanol; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 4.23 (s, 2H), 6.02 (d, 1H, J = 3.25 Hz), 7.1−8.1 (m, 7H), 8.77 (br s, *NH*), 10.13 (br s, *NH*), 11.79 (br s, *NH*); IR (KBr) 3297, 1735, 1708, 1648, 1623 cm^{-1}; MS (ES$^+$) 439.4 (MH$^+$). Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.19; H, 5.08; N, 12.75.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-(2-naphthylmethyl)-1*H*-pyrrole-2-carboxylate (12c): 54% yield; colorless needles; mp 196−7 °C from EtOAc; ^{1}H NMR (DMSO-d_6) δ 3.55 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 3.89 (s, 2H), 6.75 (d, 1H, J = 3.20 Hz), 7.2−7.9 (m, 7H), 9.58 (br s, *NH*), 11.41 (br s, *NH*), 11.81 (br s, *NH*); IR (KBr) 3322, 1728, 1697, 1641 cm^{-1}; MS (ES$^+$) 439.0 (MH+). Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.39; H, 5.13; N, 12.74.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-[(4-phenylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (12d): 87% yield; colorless needles; mp 196−7 °C from MeOH−EtOAc; ^{1}H NMR (DMSO-d_6) δ 3.55 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.78 (s, 2H), 6.75 (d, 1H, J = 3.00 Hz), 7.2−7.7 (m, 9H), 9.65 (br s, *NH*), 11.45 (br s, *NH*), 11.80 (br s, *NH*); IR (KBr) 3320, 1733, 1698, 1623 cm^{-1}; MS (ES$^+$) 465.1 (MH$^+$). Anal. Calcd for $C_{24}H_{24}N_4O_6$: C, 62.06; H, 5.20; N, 12.06. Found: C, 62.14; H, 5.20; N, 12.10.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-[(4-isopropylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (12e): 72% yield; colorless needles; mp 157−8 °C from 2-propanol; ^{1}H NMR (DMSO-d_6) δ 1.15 (d, J = 6.94 Hz, 6H), 2.81 (m, 1H), 3.54 (s, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 3.77 (s, 2H), 6.68 (d, 1H, J = 3.20 Hz), 7.00 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 9.61 (br s, *NH*), 11.44 (br s, *NH*), 11.75 (br s, *NH*); IR (KBr) 3286, 2956, 1742, 1702, 1648 cm^{-1}; MS (ES$^+$) 431.4 (MH$^+$). Anal. Calcd for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.08; N, 13.01. Found: C, 58.21; H, 6.00; N, 12.75.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-[[(4-(trifluoromethyl)phenyl]methyl]-1*H*-pyrrole-2-carboxylate (12f): 71% yield; colorless needles; mp 184−5 °C from 2-propanol; ^{1}H NMR ($CDCl_3$) 3.69 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.91 (s, 2H), 6.49 (d, 1H, J = 3.20 Hz), 7.26 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 9.04 (br s, *NH*), 9.92 (br s, *NH*), 11.64 (br s, *NH*); IR (KBr) 3303, 1731, 1697, 1652, 1624 cm^{-1}; MS (ES$^+$) 457.7 (MH$^+$). Anal. Calcd for $C_{19}H_{19}N_4O_6F_3$: C, 50.00; H, 4.20; N, 12.28. Found: C, 50.10; H, 4.21; N, 12.22.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-(cyclohexylmethyl)-1*H*-pyrrole-2-carboxylate (12g): 60% yield; colorless needles; mp 171−2 °C from 2-propanol; ^{1}H NMR ($CDCl_3$) 0.8−1.7 (m, 11H), 2.33 (d, J = 7.0, 2H), 3.67 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 6.60 (d, 1H, J = 3.24 Hz), 7.26 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 9.20 (br s, *NH*), 10.00 (br s, *NH*), 11.81 (br s, *NH*); IR (KBr) 3304, 2925, 2852, 1731, 1713, 1647, 1621 cm^{-1}; MS (ES$^+$) 395.2 (MH$^+$). Anal. Calcd for $C_{18}H_{26}N_4O_6$: C, 54.81; H, 6.64; N, 14.20. Found: C, 54.55; H, 6.67; N, 14.07.

Methyl 3-[[[(methoxycarbonyl)amino][(methoxycarbonyl)imino]methyl]amino]-4-(3-thienylmethyl)-1*H*-pyrrole-2-carboxylate (12i): 66% yield; colorless needles; mp 168−70 °C from toluene; ^{1}H NMR ($CDCl_3$) 3.71 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.86 (s, 2H), 6.55 (d, 1H, J = 3.10 Hz), 6.88 (m, 1H), 6.94 (m, 1H), 7.22 (m, 1H), 9.25 (br s, *NH*), 10.08 (br s, *NH*), 11.74 (br s, *NH*); IR (KBr) 3277, 1737, 1699, 1648, 1625 cm^{-1}; MS (ES$^+$) 395.3 (MH$^+$). Anal. Calcd for $C_{16}H_{18}N_4O_6S$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.71; H, 4.73; N, 14.25.

General Procedure for the Carbamates 13. 2-(Carbomethoxyamino)-7-(phenylmethyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*] pyrimidin-4-one (13a). From 10. The pyrrole **2a** (4.6 g, 0.02 mol) was dissolved in MeOH (20 mL), and **10** (4.5 g, 0.022 mol) was added followed by AcOH (6.0 g, 0.1 mol). The mixture was stirred at room temperature overnight and became a thick paste. NaOMe (25%) (26 mL, 0.12 mol) was added, and stirring was continued at room temperature for 2 h. The mixture was neutralized with AcOH and the solid collected by filtration and washed well with water. After drying, **13a** (4.2 g, 70%) was obtained as an off-white powder: mp >250 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.71 (s, 3H), 3.88 (s, 2H), 7.0−7.3 (m, 6H), 11.00 (br s, *NH*), 11.23 (br s, *NH*), 11.80 (br s, *NH*); IR (KBr) 3355, 1735, 1700, 1608 cm^{-1}; MS (ES$^+$) 299.3 (MH$^+$). Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.39; H, 4.73; N, 18.73. Found: C, 60.39; H, 4.80; N, 18.69. **From 11.** The use of **11** in place of **10** gave 4.5 g (76%) of **13a** as an off-white solid identical with that obtained from **10**.

Generally, the carbamates **(13)** were not characterized but were converted directly to the pyrrolopyrimidines **(1)**.

General Method for the Pyrrolopyrimidines 1. 2-Amino-7-(phenylmethyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]-pyrimidin-4-one (1a). 13a (4.54 g, 0.15 mol) was added to 1 N NaOH (46 mL), and the mixture was heated at 55 °C for 3 h. The mixture was cooled and neutralized with acetic acid, and the solid was collected by filtration. After being washed well with water and drying at 110 °C, **1a** (3.6 g, 97%) was obtained as an off-white solid: mp 276−8 °C (lit.[1] mp 269−70 °C); ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 2H), 5.85 (s, NH_2), 6.91 (d, J = 2.9 Hz, 2H), 7.1−7.3 (m, 5H), 10.39 (br s, *NH*), 11.25 (br s, *NH*); IR (KBr) 3176, 1678, 1635 cm^{-1}; MS (ES$^+$) 241.0 (MH$^+$). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.82; H, 6.16; N, 12.16.

2-Amino-7-(1-naphthylmethyl)-1,5-dihydro-4*H*-pyrrolo-[3,2-*d*]pyrimidin-4-one (1b): 74% yield; off-white solid; mp 290−2 °C; ^{1}H NMR (DMSO-d_6) δ 4.24 (s, 2H), 5.87 (s, NH_2), 6.73 (d, J = 2.9 Hz, 2H), 7.2−8.2 (m, 7H), 10.41 (br s, *NH*), 11.22 (br s, *NH*); IR (KBr) 3416, 1674 cm^{-1}; MS (ES$^+$) 291.3 (MH$^+$). Anal. Calcd for $C_{17}H_{14}N_4O\cdot0.5H_2O$: C, 68.21; H, 5.05; N, 18.72. Found: C, 68.02; H, 5.16; N, 18.60.

2-Amino-7-(2-naphthylmethyl)-1,5-dihydro-4*H*-pyrrolo-[3,2-*d*]pyrimidin-4-one (1c): 75% yield; off-white solid; mp 295 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 2H), 5.82 (s, NH_2), 6.96 (d, J = 2.9 Hz, 2H), 7.3−7.9 (m, 7H), 10.36 (br s, *NH*), 11.26 (br s, *NH*); IR (KBr) 3323, 3163, 1620 cm^{-1}; MS (ES$^+$) 291.3 (MH$^+$). Anal. Calcd for $C_{17}H_{14}N_4O\cdot0.25H_2O$: C, 69.26; H, 4.96; N, 19.00. Found: C, 69.25; H, 4.96; N, 19.05.

2-Amino-7-[(4-phenylphenyl)methyl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1d): 87% yield; off-white solid; mp >320 °C; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 2H), 5.83 (s, NH_2), 6.96 (d, J = 2.7 Hz, 2H), 7.3−7.7 (m, 9H), 10.36 (br s, *NH*), 11.25 (br s, *NH*); IR (KBr) 3406, 3176, 1654, 1623 cm^{-1}; MS (ES$^+$) 317.4 (MH$^+$). Anal. Calcd for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.09; N, 17.71. Found: C, 72.04; H, 5.16; N, 17.77.

2-Amino-7-[(4-isopropylphenyl)methyl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1e): 48% yield; off-white solid; mp 164−7 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (d, J = 6.9 Hz, 6H), 2.80 (m, 1H), 3.75 (s, 2H), 5.80 (s, NH_2), 6.89 (d, J = 2.9 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 10.34 (br s, *NH*), 11.20 (br s, *NH*); IR (KBr) 3325, 3166, 2959, 1678, 1639 cm^{-1}; MS (ES$^+$) 283.5 (MH$^+$). Anal. Calcd for $C_{16}H_{18}N_4O\cdot0.25H_2O$: C, 66.99; H, 6.50; N, 19.53. Found: C, 66.73; H, 6.53; N, 19.33.

2-Amino-7-[(4-trifluorophenyl)methyl]-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1f): 71% yield; off-white solid; mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 2H), 5.81 (br s, NH_2), 6.97 (d, J = 2.9 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 10.35 (br s, *NH*), 11.28 (br s, *NH*); IR (KBr) 3188, 1687, 1638 cm^{-1}; MS (ES$^+$) 309.3 (MH$^+$). Anal. Calcd for $C_{14}H_{11}N_4OF_3 \cdot 0.25H_2O$: C, 53.56; H, 4.82; N, 15.61. Found: C, 53.63; H, 4.45; N, 15.56.

2-Amino-7-(cyclohexylmethyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1g): 66% yield; off-white solid; mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 0.8−1.9 (m, 11H), 2.30 (d, J = 7.0 Hz), 5.76 (s, NH_2), 6.86 (d, J = 2.9 Hz, 2H), 10.27 (br s, *NH*), 11.09 (br s, *NH*); IR (KBr) 3169, 2923, 2850, 1674, 1634 cm^{-1}; MS (ES$^+$) 247.3 (MH$^+$). Anal. Calcd for $C_{13}H_{18}N_4$: C, 63.39; H, 7.37; N, 22.75. Found: C, 63.28; H, 7.32; N, 22.73.

2-Amino-7-(2-furylmethyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1h): 62% yield; off-white solid; mp 243−5 °C (lit.[1] mp 244−5 °C); ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 2H), 5.80 (s, NH_2), 5.94 (m, 1H), 6.31 (m, 1H), 6.96 (d, J = 2.9 Hz, 2H), 7.47 (m, 1H), 10.34 (br s, *NH*), 11.78 (br s, *NH*); IR (KBr) 3456, 3143, 1674, 1625 cm^{-1}; MS (ES$^+$) 231.4 (MH$^+$). Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.37; N, 24.33. Found: C, 57.23; H, 4.41; N, 24.24.

2-Amino-7-(3-thienylmethyl)-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1i): 53% yield; off-white solid; mp 258−60 °C; ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 2H), 5.84 (s, NH_2), 5.94 (m, 1H), 6.91 (d, J = 2.9 Hz, 2H), 7.04 (m, 2H), 7.39 (m, 1H), 10.37 (br s, *NH*), 11.22 (br s, *NH*); IR (KBr) 3192, 1706, 1615 cm^{-1}; MS (ES$^+$) 247.2 (MH$^+$). Anal. Calcd for $C_{11}H_{12}N_4O_2S \cdot H_2O$: C, 49.99; H, 4.58; N, 21.20. Found: C, 50.33; H, 4.60; N, 20.92.

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