3-Aminopyrroles and their application in the synthesis of pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) derivatives

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Abstract
3-Aminopyrrole derivatives have been synthesized from 3-anilino-2-cyanoacrylonitrile using Thorpe-Ziegler cyclization. These substituted pyrroles are readily converted into 5*H*-pyrrolo[3,2-*d*]pyrimidine (9-deazapurines).

Keywords: 3-Aminopyrrole, pyrrolo[3,2-*d*]pyrimidine, 9-deazapurines, *β*-enaminonitriles, Thorpe-Ziegler cyclization

Introduction

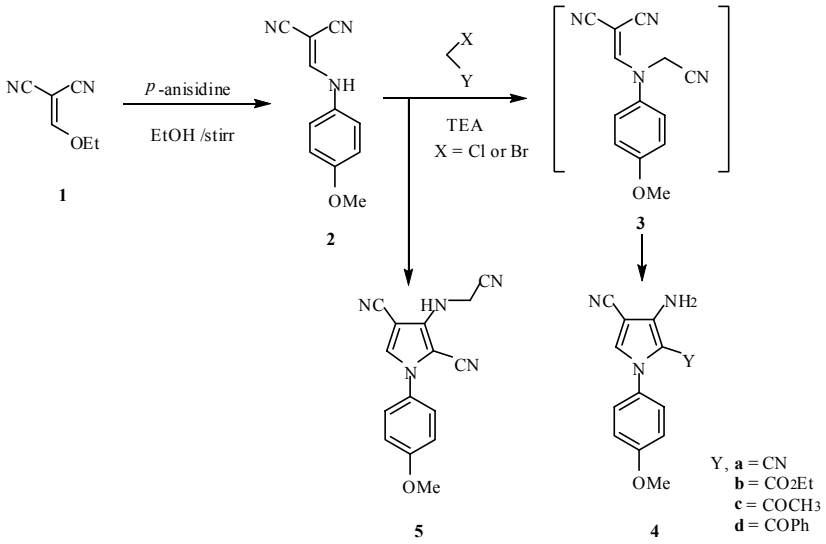
Polyfunctional derivatives of 3-aminopyrroles constitute an important family of compounds due to their wide applications as antibacterial, antiviral, anticonvulsant, anti-inflammatory, analgesic, and antipyretic activities.[1-4] Due to the importance of pyrrole for various applications, great efforts have been made towards the preparation of this heterocyclic system.[5-9] Recently we described several efficient approaches to heteroaromatic systems using functionally substituted enamine precursors.[10-14]

In continuation to our interest in the chemistry of *β,β*-enaminonitriles we report here the results of our work aimed at exploring the potential utility of 3-anilino-2-cyanoacrylonitrile in the heterocyclic synthesis. The synthesized *β,β*-enaminonitriles **2** are converted into the corresponding 3-aminopyrrole derivatives by reaction with *α*-haloketones under basic conditions, a Thorpe-Ziegler cyclization.[15,16] These substituted pyrroles are readily converted to 5*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazapurines).[17-19]

Results and Discussion

β,β-Enaminonitrile **2** was readily synthesized by the reaction of ethoxymethylene malononitrile **1** with *p*-anisidine in ethanol at room temperature.[20] Enaminonitriles **2** were found to be good candidates to obtain 3-aminopyrrole based on a Thorpe-Ziegler cyclization.[15,16] In this method, *N*-alkylation of a *β,β*-enaminonitrile was carried out using *α*-haloketones in anhydrous DMF in the presence of K_2CO_3 as the base. Moreover, compounds having an aryl substituent on the amino moiety of the enamine group were the most convenient for alkylation and spontaneous intramolecular cyclization. The presence of this group facilitates the formation of the *N*-anion required for alkylation and subsequent carbanion formation for the cyclization involving the cyano group.

The reaction of enaminonitrile **2** with chloroacetonitrile, chloroacetone, ethyl bromoacetate and *α*-bromoacetophenone in DMF/K_2CO_3 afforded the corresponding 3-aminopyrrole derivatives **4a-d** in low yield (24-45 %) *via* intermediate **3**. We prepared compound **4** by a modification of the method used by Gewald *et al*.[15, 16] using triethylamine as alkaline reagent. When the reaction was carried out in an excess of triethylamine solution, the desired 3-aminopyrrole derivatives **4a-d** are obtained in a satisfactory yield (74-91 %).



Scheme 1

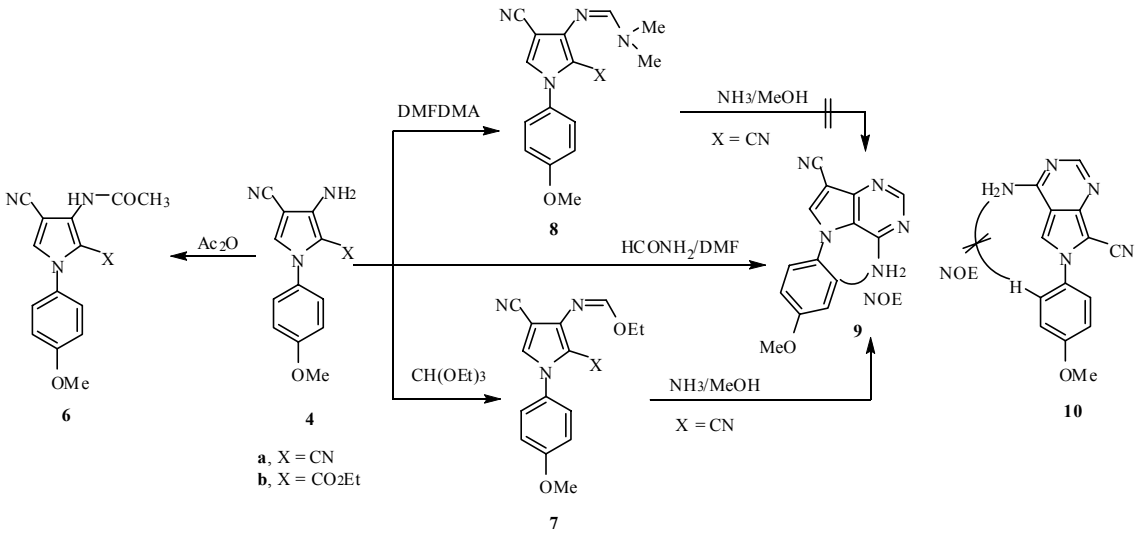
The structure of compounds **4a-d** was established on the basis of elemental analysis, IR, mass, ^{1}H and ^{13}C NMR spectral data studies (*cf*. Experimental Section). For example, the ^{1}H NMR spectrum of compound **4a** showed the absence of a signal for a methylene function and the presence of a two protons D_2O exchangeable signal at δ = 6.11 ppm for the amino function and a singlet for the pyrrole 5-H proton at δ = 7.84 ppm. ^{13}C NMR and mass spectra of compound **4a**

are in agreement with the proposed structure. When the reaction was carried out in excess of chloroacetonitrile, the *N*-substituted product **5** was obtained (Scheme 1).

The 3-amino-2-cyanopyrrole **4a** is a polyfunctional compound containing an interesting set of substituents. Although the 3-amino group has an electronegative substituent in the neighboring *ortho* position, it retains its basic properties and is readily acylated in refluxing acetic anhydride to afford the monoacetyl derivative **6**.

The most generally used approach to pyrrolo[3,2-*d*]pyrimidines has so far involved elaboration of the pyrrole ring onto a preformed pyrimidine bearing reactive functionalities at C-4 and C-5.[18,19,21] Another strategy has involved the formation of the pyrimidine ring onto a preformed 3-aminopyrrole intermediate[22] as we describe herein.

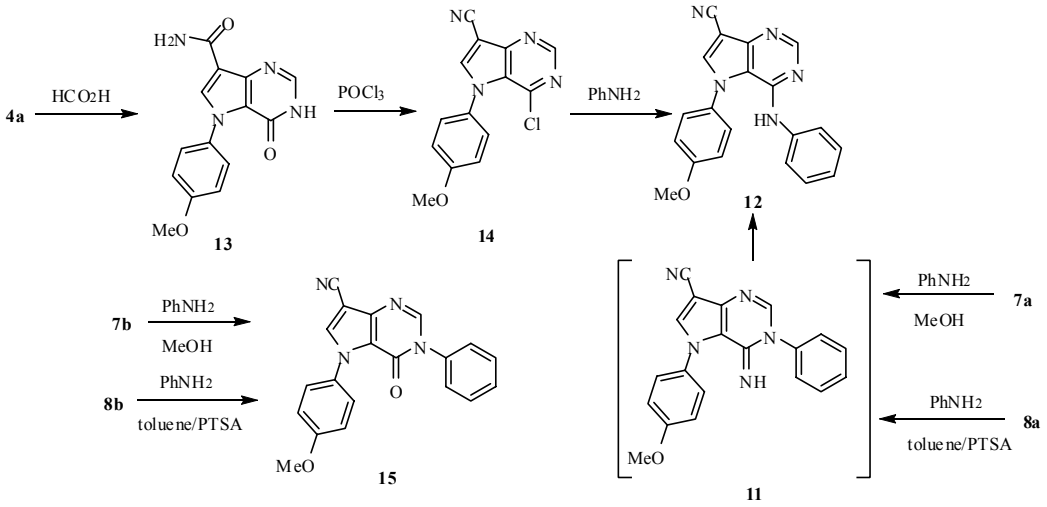
Compound **4a,b** reacted with triethyl orthoformate or dimethyl formamide dimethylacetal (DMFDMA) to give the corresponding imidocarboxylate derivatives **7** and amidine derivatives **8** respectively, which are the key compounds for the preparation of pyrrolo[3,2-*d*]pyrimidine derivatives. Thus, compound **7a** was stirred at room temperature in methanolic ammonia to produce 4-aminopyrrolopyrimidine **9** and not the isomeric form **10** (Scheme 2). Attempts to obtain **9** from **8a** according to literature methods[17] failed. The identity of pyrrolopyrimidine **9** was confirmed by ^{1}H NMR, NOE experiment and elemental analysis. Thus, the presence or absence of an Nuclear Overhauser Enhancement between specific protons allowed establishing the structure of compound **9**.



Scheme 2

Compound **9** was also obtained on heating compound **4a** in a mixture of $HCO_2H/HCONH_2/DMF$.

Following the behavior that was observed with ammonia solution, compounds **7a** and **8a** reacted with aniline under reflux to produce the Dimroth rearrangement product, 4-substituted aminopyrrolopyrimidine **12**, *via* the intermediate **11** (Scheme 3).[14,23]



Scheme 3

Based on NMR data the alternative structure **11** was excluded. The ^{1}H NMR spectra of compound **12** showed all the expected signals for aromatic protons and four singlets signals at δ = 3.86 (OCH_3), 6.98 (NH), 8.52 (2-H) and 8.62 (6-H), which was not sufficient to differentiate between structures **11** and **12**. For this reason, we obtained the HMQC and HMBC NMR spectra and made an unambiguous assignment in the ^{1}H and ^{13}C NMR spectrum (see Experimental Section).

In the HMBC spectrum, we observe an intense correlation peak for the NH proton at δ = 6.98 with the carbons peak at δ = 120.68 ppm (C-2´´, 6´´), which is characteristic only for structure **12** but not for **11**, where the indicated proton and carbon atoms are separated by five bonds.

To confirm the structure of compound **12** an independent route was followed, compound **4a** was refluxed in boiling formic acid to produce pyrrolopyrimidinone-7-carboxamide **13**. Compound **13** was refluxed in phosphorus oxychloride to obtain 4-chloropyrrolopyrimidines **14**[24], then reacting compound **14** with aniline, the pyrrolo[3,2-*d*]pyrimidine **12** (65 %) was isolated, whose spectral characteristics were completely coincident with the samples obtained before (Scheme 3).

Under the same reaction conditions, the amidines **7b** and **8b** reacted with aniline to afford the bicyclic compound 4-oxo-3-phenylpyrrolo[3,2-*d*]pyrimidine **15**. Also in these cases the ester group in position 2 of the pyrrole ring but not the 4-cyano group participates in the cyclization, as shown in the ^{1}H NMR spectra which revealed the absence of the ester groups (no triplet and quartet signals are found) and the presence of CN signal in the IR at 2232 cm^{-1} and at δ 117.02 ppm in the ^{13}C NMR spectra.

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were registered on a Perkin Elmer FTIR-1600 using Nujol emulsions between NaCl plates. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75.4 or 100.62 MHz) spectra were recorded in deuterated dimethylsulfoxide [D_6]DMSO or deuterated chloroform $CDCl_3$ on a Varian Unity Plus Spectrometer using tetramethylsilane (TMS) as an internal reference, and results are expressed as δ values. Double resonance, HMQC and HMBC experiments were carried out for complete assignment of proton and carbon signals in the NMR spectra, whenever possible. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were obtained on a Leco CHNS-932 instrument. Compound **2** was prepared according to the literature.[20]

General procedure for preparation of 3-aminopyrrole derivatives 4a-d

Method A. A mixture of **2** (0.01 mol), the α-halo compound (chloroacetonitrile, chloroacetone, ethyl bromoacetate and α-bromoacetophenone) (0.011 mol), and potassium carbonate (2.0 g) in dimethylformamide (20 mL) was stirred for 1 h, at 90 °C, in an oil-bath. The reaction mixture was cooled and poured into water (60 mL). The precipitated solid products formed were filtered off, washed thouroughly with cold water and recrystallized from EtOH to afford the corresponding cyclized products **4a** (45 %), **4b** (24%), **4c** (39%), **2d** (35%).

Method B. To a solution of the intermediate **2** (0.01 mol) the α-halo compound (chloroacetonitrile, chloroacetone, ethyl bromoacetate and α-bromoacetophenone) (0.011 mol) and triethylamine (4 mL) were added with external cooling. The reaction mixture was refluxed for 10-15 minutes, after cooling (50 mL) water was added, the solid product was filtered off, washed thoroughly with cold water and crystallized from ethanol (in case of **4a,** 91 %). For derivatives **4b-c** a brown oil was separated, the water was decanted and the oil was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated to give a solid which was crystallized from EtOH.

3-Amino-1-(4-methoxyphenyl)-1*H*-pyrrole-2,4-dicarbonitrile (4a). Yield (91%), beige solid, mp. 186-188 ºC (EtOH) [Lit. Mp. 187-188][15]; IR (Nujol): ν = 3437,3349 (NH_2), 2227, 2205 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 3.80 (s, 3H, OCH_3), 6.11 (s, 2H, NH_2), 7.07 (d, 2H, J = 8.8 Hz, H-3`, 5`), 7.41 (d, 2H, J = 8.8 Hz, H-2`, 6`), 7.84 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ = 55.56 (OCH_3), 83.23 (C-4), 88.18 (C-2), 113.38 (CN), 114.23 (CN), 114.71 (C-3`,5`), 125.44 (C-2`,6`), 130.12 (C-1`), 132.52 (C-5), 148.32 (C-3), 159.21 (C-4`). Anal. Calcd. for $C_{13}H_{10}N_4O$ (238.24): C, 65.54; H, 4.23; N, 23.52. Found: C, 65.44; H, 4.28; N, 23.44.

Ethyl 3-amino-4-cyano-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (4b). Yield (74%), white solid, mp. 163-164 ºC (EtOH) [Lit. Mp. 159-161][15]; IR (Nujol): ν = 3443, 3343 (NH_2), 2215 (CN), 1657 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 0.98 (t, 3H, J = 7.5 Hz, CH_3), 3.78 (s, 3H, OCH_3), 3.99 (q, 2H, J = 7.5 Hz, CH_2), 5.93 (s, 2H, NH_2), 6.95 (d, 2H, J = 8.7 Hz, H-3`, 5`), 7.24 (d, 2H, J = 9.0 Hz, H-2`, 6`), 7.65 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ = 13.96 (CH_3), 55.45

(OCH_3), 59.00 (CH_2), 83.26 (C-4), 105.72 (C-2), 113.53 (C-3`, 5`), 114.80 (CN),127.18 (C-2`, 6`), 132.58 (C-1`), 134.46 (C-5), 146.36 (C-3), 158.76 (C-4`), 160.03 (CO). Anal. Calcd. for $C_{15}H_{15}N_3O_3$ (285.30): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.46; H, 5.38; N, 14.43.

5-Acetyl-4-amino-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbonitrile (4c). Yield (78%), white solid, mp. 212-214 ºC (EtOH); IR (KBr): ν = 3404, 3289 (NH_2), 2222 (CN), 1688 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.63 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.68 (s, 2H, NH_2), 7.04 (d, 2H, *J* = 9 Hz, H-3`, 5`), 7.38 (d, 2H, *J* = 9 Hz, H-2`, 6`), 7.66 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ = 28.54 (CH_3), 55.53 (OCH_3), 81.59 (C-4), 114.48 (C-3`,5`), 114.68 (CN), 118.21 (C-2), 127.93 (C-2`,6`), 132.21 (C-1`), 135.21 (C-5), 147.45 (C-3), 159.38 (C-4`), 186.16 (CO). Anal. Calcd. for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.87; H, 5.13; N, 16.46. Found: C, 65.88; H, 4.94; N, 16.49.

4-Amino-5-benzoyl-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbonitrile (4d). Yield (80%), pale yellow solid, mp. 187-188 ºC (EtOH); IR (Nujol): ν = 3423, 3318 (NH_2), 2220 (CN), 1678 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.61 (s, 3H, OCH_3), 6.58 (s, 2H, NH_2), 6.64 (d, 2H, *J* = 9 Hz, Ar-H), 7.02 (d, 2H, *J* = 9 Hz, Ar-H), 7.08-7.22 (m, 5H, Ar-H), 7.83 (s, 1H, H-5). Anal. Calcd. for $C_{19}H_{15}N_3O_2$ (317.34): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.78; H, 5.14; N, 13.11.

3-(Cyanomethylamino)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,4-dicarbonitrile (5). This compound was prepared similarly to the method B used above by using 2 equivalents of chloroacetonitrile. Yield (55%); pale yellow solid, mp. 198-200 ºC (EtOH); IR (Nujol): ν = 3333 (NH), 2224, 2203 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.81 (s, 3H, OCH_3), 4.35 (d, 2H, *J* = 7 Hz, CH_2), 7.10 (d, 2H, *J* = 9 Hz, H-3`, 5`), 7.13 (s, 1H, NH), 7.47 (d, 2H, *J* = 9 Hz, H-2`, 6`), 8.05 (s, 1H, H-5); ^{13}C NMR (DMSO-d_6): δ = 32.78 (CH_2), 55.61 (OCH_3), 83.37 (C-4), 89.13 (C-2), 113.18 (CN), 113.76 (CN), 114.76 (C-3`,5`), 117.99 (CN), 126.08 (C-2`,6`), 129.65 (C-1`), 133.92 (C-5), 145.42 (C-3), 159.58 (C-4`).– MS (EI, 70 eV): *m/z* (%) = 237.08 (34), 250.08 (100), 277.09 (36, M+).

Anal. Calcd. for $C_{15}H_{11}N_5O$ (277.28): C, 64.97; H, 4.00; N, 25.26. Found: C 64.87, H 4.16, N 24.95.

Reaction with acetic anhydride

To compound **4a,b** (0.01 mol) was added acetic anhydride (10 mL), the reaction mixture was heated under reflux for 3 h, cooled and the precipitate was filtered off.

***N*-(2,4-Dicyano-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)acetamide (6a).** Yield: (72%); pale yellow solid, mp. 229-230 ºC (EtOH). IR (Nujol): ν = 320 (NH), 2236, 2226 (CN), 1671 (CO) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.09 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.12 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.52 (d, 2H, *J* = 9.0 Hz, Ar-H), 8.21 (s, 1H, H-5), 10.46 (s, 1H, NH). MS (EI, 70 eV): *m/z* (%) = 280.09 (M+, 6); 238.08 (100); 223.06 (32); 195.09 (14).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$ (280.096): C, 64.28; H, 4.32; N, 19.99. Found: C, 64.03; H, 4.30; N, 19.92.

Ethyl 3-acetamido-4-cyano-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (6b).

Yield (75%); white solid, mp. 240-241 ºC (AcOH). IR (Nujol): ν = 3237 (NH); 2238 (CN); 1714, 1672 (CO) cm^{-1}; ^1H NMR (DMSO-d_6):δ = 1.04 (t, 3H, *J* = 7.5 Hz, CH_3), 2.05 (s, 3H, CH_3), 3.79

(s, 3H, OCH_3), 4.03 (q, 2H, *J* = 7.5 Hz, CH_2), 6.99 (d, 2H, *J* = 6.9 Hz, Ar-H), 7.29 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.93 (s, 1H, H-5), 9.75 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{17}N_3O_4$ (327.33): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.25; H, 5.02; N, 12.80.

Reaction with triethyl orthoformate (7a,b)

A mixture of 3-aminopyrrole-4-carbonitrile, **4a,b** (0.015 mol), triethyl orthoformate (20 mL) was heated under reflux for 7 h and then evaporated under reduced pressure. The residue was treated with ethanol and the solid product formed was collected by filtration, washed with ethanol and crystallized from EtOH.

Ethyl *N*-2,4-dicyano-1-(4-methoxyphenyl)-1*H*-pyrrol-3-ylimidoformate (7a). Yield (84%); white solid, mp. 164-165 ºC (EtOH); IR (Nujol): ν = 2233, 2215 (CN), 1639 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.32 (t, 3H, *J* = 7.5 Hz, CH_3), 3.82 (s, 3H, OCH_3), 4.31 (q, 2H, *J* = 7.5 Hz, CH_2), 7.12 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.52 (d, 2H, *J* = 9.0 Hz, Ar-H), 8.19 (s, 1H, N=CH), 8.33 (s, 1H, H-5). - MS (EI, 70 eV): *m/z* (%) = 294.11 (58, M+); 266.08 (26); 238.08 (100); 223.06 (78). Anal. Calcd. for $C_{16}H_{14}N_4O_2$ (294.31): C, 65.30; H, 4.79; N, 19.04. Found: C, 65.74; H, 4.64; N, 18.95.

Ethyl 4-cyano-3- (ethoxymethylenamino)-1- (4-methoxyphenyl)-1*H*- pyrrole-2-carboxylate (7b). Yield (82%); white solid, mp. 171-172 ºC (EtOH); IR (Nujol): ν = 2228 (CN), 1703 (CO), 1640 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 1.00 (t, 3H, *J* = 7.5 Hz, CH_3), 1.32 (t, 3H, *J* = 7.5 Hz, CH_3), 3.79 (s, 3H, OCH_3), 3.96 (q, 2H, *J* = 7.5 Hz, CH_2), 4.29 (q, 2H, *J* = 7.5 Hz, CH_2), 6.98 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.27 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.89 (s, 1H, N=CH), 8.03 (s, 1H, H-5). Anal. Calcd for $C_{18}H_{19}N_3O_4$ (341.36): C, 63.33; H, 5.61; N, 12.31. Found C, 63.17; H, 5.41; N, 12.34.

Reaction with DMFDMA

DMFDMA (0.012 mol) was added to a solution of 3-aminopyrrole-4-carbonitrile **4a,b** (0.01 mol), in dry toluene (40 mL) and the mixture heated under reflux for 7 h. the reaction mixture was cooled and the precipitated solid was filtered off and crystallized from EtOH.

***N*'-(2,4-Dicyano-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-*N*,*N*-dimethyl imioformamide (8a).** Yield (84%); beige solid, mp. 171-172 ºC (EtOH); IR (Nujol): ν = 2233, 2210 (CN), 1640 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 3.09 (s, 6H, $2CH_3$), 3.87 (s, 3H, OCH_3), 7.01 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.23 (s, 1H, N=CH), 7.34 (d, 2H, *J* = 6.9 Hz, Ar-H), 8.04 (s, 1H, H-5). Anal. Calcd. for $C_{16}H_{15}N_5O$ (293.32): C, 65.52; H, 5.15; N, 23.88. Found: C, 65.18; H, 5.00; N, 23.95.

Ethyl 4-cyano-3-((dimethylamino)methylenamino)-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (8b). Yield (71%); colorless crystals, mp. 122-123 ºC (EtOH); IR (Nujol): ν = 2212 (CN), 1686 (CO), 1630 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.97 (t, 3H, *J* = 7.5 Hz, CH_3), 2.93 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.92 (q, 2H, *J* = 7.5 Hz, CH_2), 6.96 (d, 2H, *J* = 9 Hz, Ar-H), 7.22 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.70 (s, 1H, N=CH), 7.75 (s, 1H, H-5). Anal. Calcd. for $C_{18}H_{20}N_4O_3$ (340.38): C, 63.52; H, 5.92; N, 16.46. Found: C, 63.31; H, 5.83; N, 16.40.

4-Amino-5-(4-methoxyphenyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carbonitrile (9)

Method A. Amidine **7a** (2.0 mmol) was added to a mixture of methanol (15 mL) and 25% aqueous ammonia solution (15 mL). The reaction mixture was stirred for 3 h, cooled, and the precipitated solid was filtered off and crystallized from EtOH-DMF, 2:1.

Method B. A mixture of 3-amino-2-cyanopyrrole **4a** (0.01 mol), formamide (15 mL), DMF (5 mL), and formic acid (2 mL) was heated under reflux for 6–8 h. The reaction mixture was allowed to stand overnight at room temperature. The solid obtained was filtered, washed with cold methanol, dried, and crystallized from EtOH-DMF, 2:1. Yield (74%); colorless crystals, mp. 281-282 ºC (EtOH-DMF); IR (Nujol): ν = 3400, 3293 (NH_2), 2224 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 3.84 (s, 3H, OCH_3), 6.03 (brs, 2H, NH_2), 7.14 (d, 2H, *J* = 9.0 Hz, H-3`, 5`), 7.52 (d, 2H, *J* = 9.0 Hz, H-2`, 6`), 8.29 (s, 1H, H-2), 8.46 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ = 55.61 (OCH_3), 86.44 (C-7), 113.64 (C-7a), 114.39 (CN), 114.86 (C-3`,5`), 127.81 (C-2`,6`), 129.945 (C-1`), 139.64 (C-6), 148.38 (C-4a), 150.76 (C-4), 152.63 (C-2), 159.88 (C-4`).- MS (EI, 70 eV): *m/z* (%) = 265.09 (100); 266.10 (13); 264.09 (40); 250.07 (50). Anal. Calcd. for $C_{14}H_{11}N_5O$ (265.27): C, 63.39; H, 4.18; N, 26.40. Found: C, 63.48; H, 3.99; N, 26.12.

5-(4-Methoxyphenyl)-4-(phenylamino)-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carbonitrile (12)

Method A. To a solution of amidine **7a** (3.0 mmol) in methanol (20 mL) was added aniline (3.0 mmol). The reaction mixture was heated under reflux for 7 h. The precipitate formed after cooling overnight was filtered off and dried and recrystallized from ethanol (82 %).

Method B. Aniline (2.0 mmol) and *p*-toluenesulfonic acid (0.01 g) were added to a solution of amidine **8a** (2.0 mmol) in toluene (40 mL). The reaction mixture was refluxed for 7 h, and the precipitated solid was filtered off and crystallized from EtOH (77 %).

Method C. To a solution of 4-chloropyrrolopyrimidine 14 (2.0 mmol) in methanol (20 mL) was added aniline (2.0 mmol). The reaction mixture was refluxed for 5 h. The precipitate formed during reflux was filtered off and found identical in all respect with that obtained from method A (65 %).

Yield (77%); colorless crystals, mp. 225-226 ºC (EtOH-DMF); IR (Nujol): ν = 3216 (NH), 2228 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 3.86 (s, 3H, OCH_3), 6.98 (s, 1H, NH), 7.03 (t, 1H, *J* = 7.5 Hz, H-4´´), 7.18 (d, 2H, *J* = 8.7 Hz, H-3´, 5´), 7.28 (t, 2H, *J* = 7.5 Hz, H-3´´, 5´´), 7.33 (d, 2H, *J* = 8.7 Hz, H-2´´, 6´´), 7.65 (d, 2H, *J* = 8.7Hz, H-2´, 6´), 8.52 (s, 1H, H-2), 8.62 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ = 55.75 (OCH_3), 86.91 (C-7), 114.11 (C-7a), 114.14 (CN), 114.84 (C-3`,5`), 120.69 (C-2´´, 6´´), 123.42 (C-4´´), 128.06 (C-2`,6`), 128.76 (C-3´´, 5´´), 129.84 (C-1`), 138.35 (C-1´´), 140.49 (C-6), 147.39 (C-4), 148.78 (C-4a), 151.94 (C-2), 160.04 (C-4`).- MS (EI, 70 eV): *m/z* (%) = 342.13 (8); 341.12 (46, M+); 340.12 (100); 325.10 (13); 297.10 (13). Anal. Calcd. for $C_{20}H_{15}N_5O$ (341.37): C, 70.37; H, 4.43; N, 20.52. Found: C, 70.42; H, 4.36; N, 20.63.

5-(4-methoxyphenyl)-4-oxo-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxamide (13)

A mixture of 3-amino-2-cyanopyrrole **4a** (0.01 mol) and formic acid (25 mL) was stirred at reflux temperature for 8 h. The reaction mixture was then allowed to cool, poured onto crushed

ice (50 g), neutralized with sodium hydroxide solution (2 N), filtered, dried, and crystallized from a mixture of EtOH-DMF, (2:1).
Yield (77%); white solid, mp. 318-320ºC (EtOH-DMF); IR (Nujol): ν = 3376 (NH_2), 3179 (NH) cm^{-1}; ^1H NMR (DMSO-d_6):δ = 3.81 (s, 3H, OCH_3), 7.01 (d, 2H, *J* = 9.0 Hz, H-3′, 5′), 7.44 (d, 2H, *J* = 9.3 Hz, H-2′, 6′), 7.48 (s, 1H, NH, D_2O exchange), 7.86 (s, 1H, NH, D_2O exchange), 7.90 (s, 1H, H-2), 8.06 (s, 1H, H-6), 12.35 (s, 1H, NH, D_2O exchange). MS (EI, 70 eV): *m/z* (%) = 285.09 (15); 284.09 (100, M+); 269.08 (12); 268.07 (65); 266.08 (100); 251.06 (32). Anal. Calcd. for $C_{14}H_{12}N_4O_3$ (284.27): C, 59.15; H, 4.25; N, 19.71. Found: C, 59.26; H, 4.34; N, 19.31.

4-Chloro-5-(4-methoxyphenyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carbonitrile (14)
A mixture of pyrrolopyrimidin-4-one **13** (0.01 mol) and phosphorus oxychloride (25 mL) was refluxed for 9 h. After the completion of reaction, the excess of phosphorus oxychloride was removed under vacuum. The cooled reaction mixture was then added to crushed ice (25 g). The resulting solid was filtered, washed with sodium bicarbonate (5 % w/v) followed by cold water, dried, and crystallized from ethanol and chloroform (8 : 2 v\v). Yield (64%); beige solid, mp. 206-208 ºC (EtOH). IR (Nujol): ν = 2230 (CN) cm^{-1}; ^1H NMR (DMSO-d_6):δ = 3.84 (s, 3H, OCH_3), 7.10 (d, 2H, *J* = 9.0 Hz, H-3′, 5′), 7.57 (d, 2H, *J* = 9.0 Hz, H-2′, 6′), 8.89 (s, 1H, H-2), 8.95 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ = 55.59 (OCH_3), 86.87 (C-7), 113.18 (CN), 114.05 (C-3`,5`), 124.22 (C-7a), 129.24 (C-2`,6`), 129.33 (C-1`), 143.46 (C-4a), 145.23 (C-6), 150.85 (C-4), 151.50 (C-2), 160.14 (C-4`). Anal. Calcd. for $C_{14}H_9ClN_4O$ ⅓H_2O C, 57.79; H, 3.09; N, 19.26. Found: 58.00; 3.40; 18.96.

5-(4-Methoxyphenyl)-4-oxo-3-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carbonitrile (15)
Method A. To a solution of amidine **7b** (3.0 mmol) in methanol (20 mL) was added aniline (3.0 mmol). The reaction mixture was heated under reflux for 7 h. The precipitate formed after cooling overnight was filtered off and dried and recrystallized from ethanol (71 %).
Method B. Aniline (2.0 mmol) and *p*-toluenesulfonic acid (0.01 g) were added to a solution of amidine **8b** (2.0 mmol) in toluene (40 mL). The reaction mixture was refluxed for 7 h, and the precipitated solid was filtered off and crystallized from EtOH (66 %).
Yield (71 %); white solid, mp. 258-260 ºC (EtOH-DMF); IR (Nujol): ν = 2232 (CN), 1697 (CO) cm^{-1}; ^1H NMR (DMSO-d_6):δ = 3.79 (s, 3H, OCH_3), 7.00 (d, 2H, *J* = 8.7 Hz, H-3′, 5′), 7.40-7.60 (m, 7H, Ar-H), 8.35 (s, 1H, H-2), 8.50 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6): δ = 55.52 (OCH_3), 87.86 (C-7), 113.66 (C-3`,5`), 113.76 (C-7a), 117.02 (CN), 127.29 (C-2′′, 6′′), 127.72 (C-3′′, 5′′), 128.86 (C-4′′), 129.10 (C-2`,6`), 130.52 (C-1`), 137.00 (C-1′′), 138.41 (C-6), 145.49 (C-4a), 147.50 (C-2), 152.00 (C-4,C=O), 159.21 (C-4`). Anal. Calcd. for $C_{20}H_{14}N_4O_2$ 1/6H_2O C, 69.49; H, 4.05; N, 16.21. Found C, 69.26; 4.14; 16.11.

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