Enaminonitriles in Heterocyclic Synthesis: Novel Synthesis of 3-Aminopyrroles and Pyrrolo[3,2-*d*]pyrimidine Derivatives

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Several new 3-aminopyrrole derivatives have been synthesized from 3-substituted amino-2-phenylacrylonitriles using Thorpe-Ziegler cyclization. These substituted pyrroles are readily converted into 5*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazapurines).

Key words: 3-Aminopyrrole, Pyrrolo[3,2-*d*]pyrimidine, 9-Deazapurines, β-Enaminonitriles, Thorpe-Ziegler Cyclization

Introduction

Derivatives of 3-aminopyrroles have been shown to exhibit antibacterial, antiviral, anticonvulsant, anti-inflammatory, analgesic, and antipyretic activities [1 – 4]. In view of the importance of pyrrole for various applications, great efforts have been made towards preparation of this heterocyclic system [5 – 9]. Recently we described several efficient approaches to heteroaromatic systems using functionally substituted enamine precursors [10 – 17]. In conjunction with our interest in the chemistry of enaminonitriles we report here results of our work aimed to exploring the potential utility of 2-phenyl-3-piperidin-1-ylacrylonitrile in heterocyclic synthesis. The synthesized β-enaminonitriles **5** are converted into the corresponding 3-aminopyrrole derivatives by reaction with α-haloketones under basic conditions in a Thorpe-Ziegler cyclization [18, 19]. These substituted pyrroles are readily converted to 5*H*-pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) [20]. In our chemical reactivity studies described here, we principally employed the intermediates **5b** and **9a** due to their easy preparation and good yield of their reactions.

Result and Discussions

One of the main important routes to enamines is condensation of dimethyl-formamide dimethylacetal (DMFDMA) with activated methyl or methylene compounds [10 – 12]. However, under a variety of conditions the condensation of DMFDMA with benzyl cyanide did not yield the enamine **3**. Alternatively, a procedure similar to that reported recently [15] was applied. In this method the active methylene group of benzyl cyanide was condensed with piperidinyl-1-formamide diethylacetal (**2**), formed *in situ* from piperidine and triethyl orthoformate, to afford the enaminonitrile **3** in 70 % yield (Scheme 1).

The reaction of aniline derivatives with compound **3** in refluxing methanol afforded only the α-formyl phenylacetonitrile (**4**), m. p. 157 – 159 °C (159 – 160 °C [21]). On the other hand, the reaction of **3** with aromatic amines in toluene, in the presence of *p*-toluenesulfonic acid, produced the enaminonitriles **5a – c** with elimination of piperidine. Compound **3** reacted also with 2-aminopyrazole and 2-aminobenzimidazole to yield cyclic products **6** and **7**, respectively. Establishing of the structures of **5 – 7** was based on their spectral analysis.

Enaminonitriles **5** were found to be good candidates to obtain 3-aminopyrroles based on a Thorpe-Ziegler cyclization [18, 19]. In this method, *N*-alkylation of a β-enaminonitrile was carried out using α-haloketones in anhydrous DMF in the presence of K_2CO_3 as an alkaline reagent. Moreover, compounds having an aryl substitutent on the amino moiety of the enamine group were the best for alkylation and subsequent 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.

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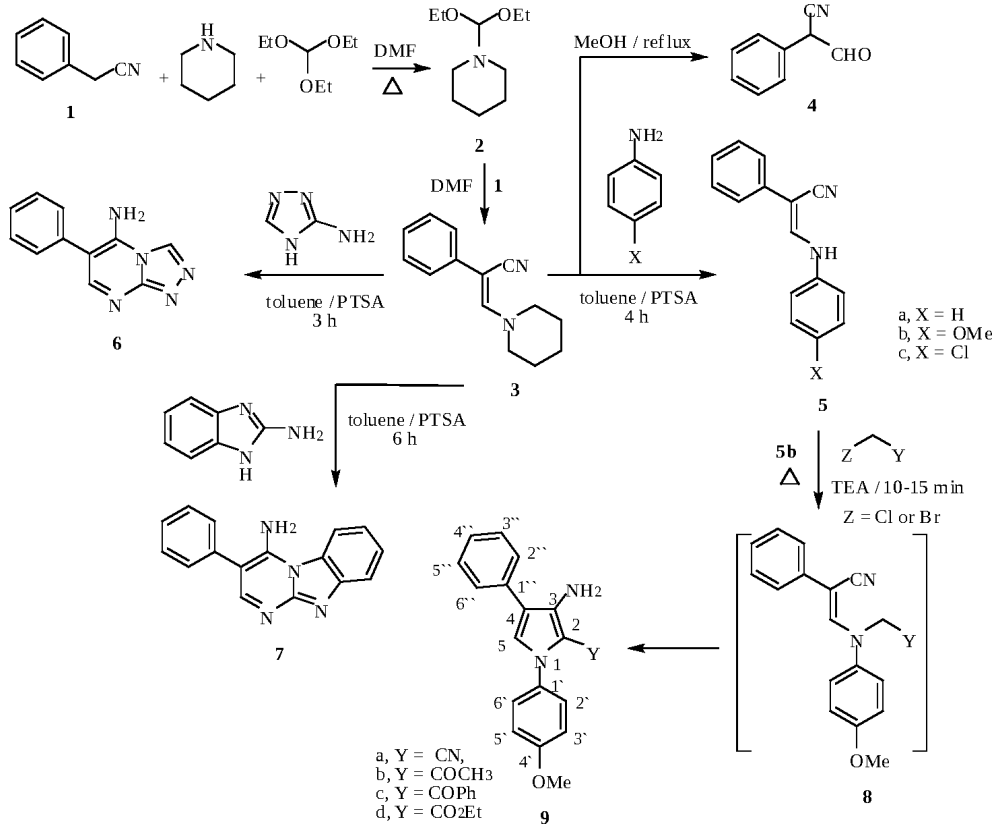
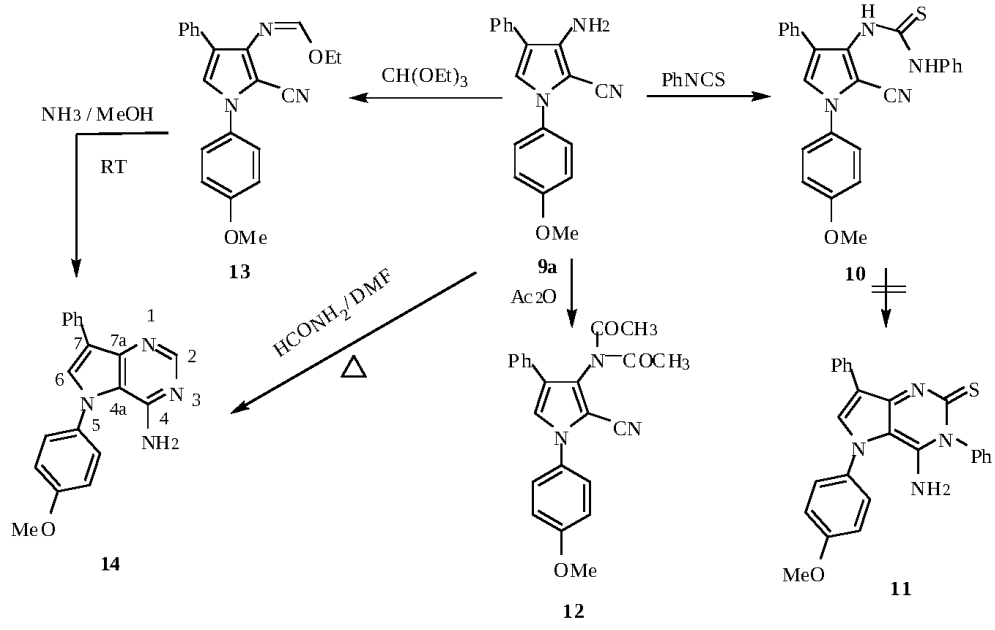


Scheme 1.

The reactions of enaminonitrile **5** with chloroacetonitrile, chloroacetone, bromoacetic acid ester and α-bromoacetophenone in DMF/K_2CO_3 afforded the corresponding 3-aminopyrrole derivatives **9** in low yield (35 – 54 %) *via* the nonisolable intermediates **8**. When the reaction was carried out in a solution of excess of triethylamine the desired 3-aminopyrrole derivatives **9** were obtained in satisfactory yield (70 – 86 %). The structure of compounds **9a – d** was established on the basis of elemental analysis, IR, mass, ^{1}H and ^{13}C NMR spectral data (*cf.* Experimental Section). For example, the ^{1}H NMR spectrum of compound **9a** showed the absence of a signal for a methylene function and the presence of two D_2O exchangeable protons at δ = 6.14 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 **9a** are in accordance with the proposed structure.

In recent years, urea and thiourea derivatives [22 – 24] have emerged as structurally novel anticonvulsant agents. Compound **9a** reacted readily with phenylisothiocyanate to yield the thiourea derivative **10**. Trials to cyclize the latter into pyrrolopyrimidine **11** failed (Scheme 2). The 3-amino-2-cyanopyrrole **9a** 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 basic properties and is readily acylated in refluxing acetic anhydride to afford the diacetyl derivative **12**.

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 [25]. Another strategy has involved the formation of the pyrimidine ring onto a preformed 3-aminopyrrole intermediate [26] as we describe herein. Compound **9a** reacted with triethyl orthoformate to give the corresponding ethoxymethylene amino derivative **13** which is the key compound for the preparation of pyrrolo[3,2-*d*]pyrimidine derivatives. Thus, compound **13** was stirred at r. t. in methanolic ammonia to produce 4-aminopyrr-



Scheme 2.

olopyrimidine **14** (Scheme 2). The identity of pyrrolopyrimidine **14** was confirmed by ^{1}H NMR and elemental analysis. A similar closure of the pyrimidine ring using ammonia in the synthesis of 4-amino-pyrrolopyrimidine **13** was successfully effected on heating compound **9a** in a mixture of $HCO_2H/HCONH_2$/DMF.

Heating the ethoxymethylene amino derivative **13** with *p*-chloroaniline led to the formation of the Dimroth-rearrangement product, 4-substituted aminopyrrolopyrimidine **16**, *via* the intermediate **15** (Scheme 3) [17, 27]. The alternative structure **15** was excluded based on NMR data. The 1D ^{1}H NMR spectra of compound **16** showed all the expected signals for aromatic protons and four singlets at δ = 3.86 (OCH_3), 6.98 (NH), 8.51 (2-H) and 8.62 (6-H), respectively, but this was not sufficient to differentiate between structures **15** and **16**. 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 carbon peak at δ = 122.52 ppm (C-b,f), which is characteristic only of structure **16** but not of **15**, where the indicated proton and carbon atoms are separated by five bonds.

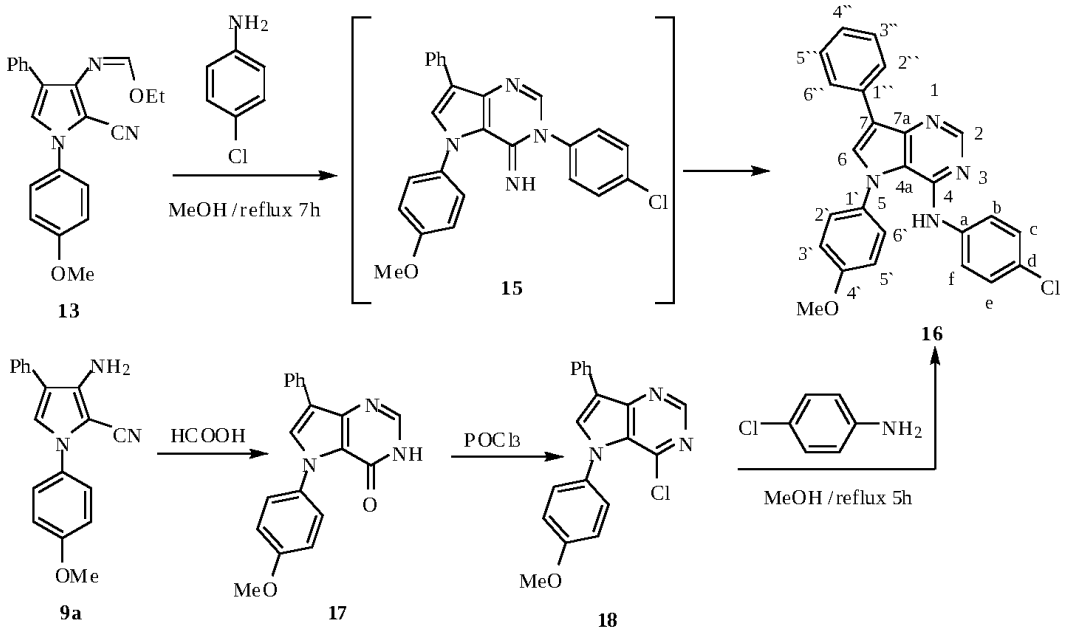
To confirm the structure of compound **16** an independent synthetic route was followed. Compound **9a** was refluxed in boiling formic acid to produce pyrrolopyrimidinone **17**. Compound **17** was refluxed in phosphorus oxychloride to obtain the 4-chloropyrrolopyrmidine **18** [28]. Reacting compound **18** with *p*-chloroaniline gave the pyrrolo[3,2-*d*]pyrimidine **16** (68 %) whose spectral characteristics were completely coincident with those of samples obtained before (Scheme 3).

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were registered on a Perkin Elmer FTIR-1600 instrument using KBr discs or Nujol emulsions between NaCl plates. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded in deuterated dimethylsulfoxide [D_6]DMSO 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 obtained on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Elemental analyses were obtained on a Leco CHNS-932 instrument.

*2-Phenyl-3-piperidin-1-yl-acrylonitrile (**3**)*

To a mixture of benzyl cyanide **1** (0.3 mol), triethyl orthoformate (0.32 mol) and piperidine (0.3 mol) DMF (40 mL) was added, and the solution was refluxed for 72 h. The re-



Scheme 3.

action mixture was then cooled and poured onto water. The solid product formed was collected by filtration and crystallized from ethanol. M. p. 115 – 116 °C. – Yield: 70 %. – IR (KBr): ν = 2190 (CN), 1616 (C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.60 (s, 6H, $3CH_2$), 3.63 (s, 4H, $2CH_2$), 7.16 (s, 1H, olefinic-H), 7.26 – 7.45 (m, 5 H, Ar-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 24.36, 26.41, 51.96, 75.41 (*C*=CH), 121.59 (CN), 124.48, 125.51, 129.14, 137.27, 149.29 (C=*C*H). – MS (EI, 70 eV): *m/z* (%) = 212 (42) $[M]^+$. – $C_{14}H_{16}N_2$ (212.29): calcd. C 79.21, H 7.60, N 13.20; found C 79.29, H 7.67, N 13.17.

General procedure for the preparation of 3-arylamino-2-phenylacrylonitrile derivatives ***5a – c****, triazolopyrimidine (****6****) and pyrimidobenzimidazole (****7****)*

An aromatic or heteroaromatic amine (0.01 mol) and *p*-toluenesulfonic acid (0.15 g) were added to a solution of an enaminonitrile **3** (0.01 mol) in toluene (40 mL). The reaction mixture was refluxed for 7 h, and the precipitated solid was collected by filtration, then crystallized from the proper solvent, to afford **5a – c**, **6** and **7**, respectively.

*2-Phenyl-3-(phenylamino)acrylonitrile (****5a****)*

M. p. 165 – 166 °C (EtOH). Yield: 70 %. – IR (KBr): ν = 2202 (CN), 1617 (C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.02 (t, 1H, *J* = 7 Hz, Ar-H), 7.16 (t, 1H, *J* = 7 Hz, Ar-H), 7.30 – 7.52 (m, 8H, Ar-H), 8.08 (brs, 1H, olefinic-H), 9.68 (brs, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 220 (78) $[M]^+$. – $C_{15}H_{12}N_2$ (220.28): calcd. C 81.79, H 5.49, N 12.72; found C 81.97, H 5.61, N 12.89.

*3-(4-Methoxyphenylamino)-2-phenylacrylonitrile (****5b****)*

M. p. 128 – 130 °C (EtOH). Yield: 89 %. – IR (KBr): ν = 2198 (CN), 1614 (C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.71 (s, 3H, OCH_3), 6.87 (d, 2H, *J* = 9 Hz, Ar-H), 7.15 (t, 1H, *J* = 7.9 Hz, Ar-H), 7.29 – 7.35 (m, 4H, Ar-H), 7.48 (d, 2H, *J* = 9 Hz, Ar-H), 8.01 (d, 1H, *J* = 13.5 Hz, olefinic-H), 9.59 (d, 1H, *J* = 13.5 Hz, NH). – MS (EI, 70 eV): *m/z* (%) = 250 (91) $[M]^+$. – $C_{16}H_{14}N_2O$ (250.30): calcd. C 76.78, H 5.64, N 11.19; found C 76.51, H 5.80, N 11.05.

*3-(4-Chlorophenylamino)-2-phenylacrylonitrile (****5c****)*

M. p. 145 – 146 °C (EtOH). Yield: 74 %. – IR (KBr): ν = 2204 (CN), 1618 (C=C) cm^{-1}. – ^1H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 7.18 (d, 2H, *J* = 9 Hz, Ar-H), 7.21 – 7.33 (m, 5H, Ar-H), 7.42 (d, 2H, *J* = 9 Hz, Ar-H), 8.15 (d, 1H, *J* = 13.4 Hz, olefinic-H), 9.65 (d, *J* = 13.4 Hz, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 254 (100) [M, $^{35}Cl]^+$, 256 (26) [M, $^{37}Cl]^+$. – $C_{15}H_{11}ClN_2$ (254.71): calcd. C 70.73, H 4.35, N 11.00; found C 70.47, H 4.58, N 11.22.

*6-Phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-5-amine (****6****)*

M. p. 262 – 264 °C (EtOH-DMF, 2 : 1). Yield: 64 %. – IR (KBr): ν = 3420, 3238 (NH_2) cm^{-1}. – ^1H NMR (300 MHz,

[D_6]DMSO, 25 °C, TMS): δ = 7.23 – 7.31 (m, 1H, Ar-H), 7.38 – 7.44 (m, 4H, Ar-H), 7.90 (s, 2H, NH_2), 8.27 (s, 1H, 7-H), 8.49 (s, 1H, 4-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 104.95 (C-1a), 124.32 (C-4′), 127.71 (C-3′,5′), 129.17 (C-2′,6′), 133.22 (C-1′), 146.50 (C-6), 154.04 (C-7), 154.83 (C-4), 155.12 (C-5). – MS (EI, 70 eV): *m/z* (%) = 211 (77) $[M]^+$. – $C_{11}H_9N_5$ (211.22): calcd. C 62.55, H 4.29, N 33.16; found C 62.91, H 4.37, N 33.31.

*3-Phenylpyrimido[1,2-a]benzimidazol-4-amine (**7**)*

M. p. 220 – 222 °C (EtOH-DMF, 2 : 1). Yield: 51 %. – IR (KBr): ν = 3405, 3251 (NH_2) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 6.85 (s, 2H, NH_2), 7.01 – 7.14 (m, 2H, Ar-H), 7.26 – 7.30 (m, 1H, Ar-H), 7.42 – 7.50 (m, 4H, Ar-H), 7.52 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.98 (d, 1H, *J* = 8.5 Hz, Ar-H), 8.42 (s, 1H, 2-H). – MS (EI, 70 eV): *m/z* (%) = 260 (40) $[M]^+$. – $C_{16}H_{12}N_4$ (260.29): calcd. C 73.83, H 4.65, N 21.52; found C 73.52, H 4.47, N 21.28.

*General procedure for preparation of 3-aminopyrrole derivatives **9a** – **d***

Method A: A mixture of **5b** (0.01 mol), an α-halo compound (chloroacetonitrile, chloroacetone, bromoacetic acid ester and α-bromoacetophenone) (0.011 mol), and potassium carbonate (2.0 g) in dimethylformamide (20 mL) was stirred for 1 h at an oil bath temperature of 90 °C. The reaction mixture was cooled and poured into water (60 mL). The precipitated solid products formed were filtered off, washed several times with cold water and recrystallized from EtOH to afford the corresponding cyclized products **9a** – **d** (35 – 54 %).

Method B: To the intermediate **5b** (0.01 mol), an α-halo compound (chloroacetonitrile, chloroacetone, bromoacetic acid ester and α-bromoacetophenone) (0.011 mol) and triethylamine (4 mL) were added with external cooling. The reaction mixture was refluxed for 10 – 15 min, after cooling water (50 mL) was added, the solid product was filtered off, washed several times with cold water and crystallized from ethanol (in case of **9a**, 86 %). For the other cases **9b** – **c**, brown sticky oils separated, the water was decanted and the oil washed several times with cold water, then dissolved in ethanol and boiled for 3 min, filtered and left to cool over night. The solid products so formed were filtered off and were found pure enough for analyses.

*3-Amino-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrole-2-carbonitrile (**9a**)*

M. p. 202 – 204 °C. Yield: 86 %. – IR (KBr): ν = 3450 – 3358 (NH_2), 2217 (CN) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.79 (s, 3H, OCH_3), 6.14 (s, 2H, NH_2), 7.06 (d, 2H, *J* = 9.5 Hz, Ar-H), 7.12 (t, 1H, *J* = 8.5 Hz, Ar-H), 7.41 (d, 2H, *J* = 9.5 Hz, Ar-H), 7.45 – 7.53 (m, 4H, Ar-H), 7.84 (s, 1H, 5-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 55.65 (OCH_3), 98.98 (C-2), 113.23 (CN), 114.71 (C-3′,5′), 120.72 (C-2″,6″), 123.42 (C-4″), 125.44 (C-2′,6′), 128.86 (C-3″,5″), 130.12 (C-1′), 132.52 (C-5), 136.84 (C-1″), 142.23 (C-4), 144.32 (C-3), 159.21 (C-4′). – MS (EI, 70 eV): *m/z* (%) = 289 (66) $[M]^+$. – $C_{18}H_{15}N_3O$ (289.33): calcd. C 74.72, H 5.23, N 14.52; found C 74.58, H 5.57, N 14.79.

*1-(3-Amino-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-2-yl)ethanone (**9b**)*

M. p. 192 – 193 °C. Yield: 77 %. – IR (KBr): ν = 3440 – 3348 (NH_2), 1678 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.23 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.67 (s, 2H, NH_2), 7.03 (d, 2H, *J* = 9 Hz, Ar-H), 7.09 (t, 1H, *J* = 9 Hz, Ar-H), 7.36 (d, 2H, *J* = 9 Hz, Ar-H), 7.42 – 7.55 (m, 4H, Ar-H), 7.65 (s, 1H, 5-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 28.52 (CH_3), 55.53 (OCH_3), 114.28 (C-3′,5′), 118.20 (C-2), 122.12 (C-2″,6″), 127.93 (C-2′,6′), 128.51 (C-4″), 132.21 (C-1′), 133.62 (C-3″,5″), 135.21 (C-5), 138.64 (C-1″), 143.31 (C-4), 147.45 (C-3), 159.38 (C-4′), 186.21 (C=O). – MS (EI, 70 eV): *m/z* (%) = 306 (80) $[M]^+$. – $C_{19}H_{18}N_2O_2$ (306.36): calcd. C 74.49, H 5.92, N 9.14; found C 74.79, H 6.18, N 9.42.

*(3-Amino-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-2-yl)(phenyl)methanone (**9c**)*

M. p. 224 – 226 °C. Yield: 72 %. – IR (KBr): ν = 3452 – 3367 (NH_2), 1690 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.61 (s, 3H, OCH_3), 6.58 (s, 2H, NH_2), 6.84 (d, 2H, *J* = 9 Hz, Ar-H), 7.14 (d, 2H, *J* = 9 Hz, Ar-H), 7.20 – 7.26 (m, 4H, Ar-H), 7.30 – 7.38 (m, 6H, Ar-H), 7.83 (s, 1H, 5-H). – MS (EI, 70 eV): *m/z* (%) = 368 (42) $[M]^+$. – $C_{24}H_{20}N_2O_2$ (368.43): calcd. C 78.24, H 5.47, N 7.60; found C 78.54, H 5.19, N 7.96.

*Ethyl 3-amino-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrole-2-carboxylate (**9d**)*

M. p. 153 – 155 °C. Yield: 62 %. – IR (KBr): ν = 3492 – 3380 (NH_2), 1715 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 0.98 (t, 3H, *J* = 7.5 Hz, CH_3), 3.78 (s, 3H, OCH_3), 4.04 (q, 2H, *J* = 7.5 Hz, CH_2), 5.94 (s, 2H, NH_2), 6.93 (d, 2H, *J* = 9 Hz, Ar-H), 7.21 (d, 2H, *J* = 9 Hz, Ar-H), 7.28 (t, 1H, *J* = 8 Hz, Ar-H), 7.31 – 7.39 (m, 4H, Ar-H), 7.66 (s, 1H, 5-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 14.12 (CH_3), 55.44 (OCH_3), 59.10 (CH_2), 108.72 (C-2), 113.53 (C-3′,5′), 121.23 (C-2″,6″), 127.21 (C-2′,6′), 127.94 (C-4″), 132.14 (C-1′), 132.92 (C-3″,5″), 134.54 (C-5), 137.31 (C-1″), 141.96 (C-4), 146.41 (C-3), 158.86 (C-4′), 160.32 (C=O). – MS (EI, 70 eV): *m/z* (%) = 336 (27) $[M]^+$. – $C_{20}H_{20}N_2O_3$ (336.38): calcd. C 71.41, H 5.99, N 8.33; found C 71.58, H 6.16, N 8.59.

*1-(2-Cyano-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-3-yl)-3-phenylthiourea (**10**)*

To a solution of (0.01 mol) **9a** in dry acetone (20 mL) was added phenyl isothiocyanate (0.01 mol), and the reaction mixture was refluxed for 3 h. The reaction mixture was allowed to cool to r. t., and the solid formed was collected by filtration and crystallized from ethanol/DMF (2 : 1) to afford (**10**). M. p. 242 – 244 °C. Yield: 64 %. – IR (Nujol): ν = 2195 (CN), 3260 (NH), 1668 (C=S) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.61 (s, 3H, OCH_3), 6.86 (d, 2H, J = 9 Hz, Ar-H), 7.03 (d, 2H, J = 9 Hz, Ar-H), 7.32 – 7.53 (m, 10H, Ar-H), 7.88 (s, 1H, NH), 7.93 (s, 1H, 5-H), 8.20 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 424 (36) $[M]^+$. – $C_{25}H_{20}N_4OS$ (424.52): calcd. C 70.73, H 4.75, N 13.20, S 7.55; found C 70.41, H 4.70, N 13.54, S 7.96.

*N-Acetyl-N-(2-cyano-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-3-yl)acetamide (**12**)*

To compound **9a** (0.01 mol) was added acetic anhydride (10 mL), the reaction mixture was heated under reflux for 3 h, cooled and the precipitate filtered off. M. p. 131 – 132 °C. Yield: 67 %. – IR (Nujol): ν = 2206 (CN), 1678 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 2.27 (s, 6H, $2CH_3$), 3.80 (s, 3H, OCH_3), 7.10 (d, 2H, J = 9 Hz, Ar-H), 7.30 – 7.35 (m, 2H, Ar-H), 7.36 – 7.51 (m, 3H, Ar-H), 7.56 (d, 2H, J = 9 Hz, Ar-H), 8.06 (s, 1H, 5-H). – MS (EI, 70 eV): *m/z* (%) = 373 (54) $[M]^+$. – $C_{22}H_{19}N_3O_3$ (373.40): calcd. C 70.76, H 5.13, N 11.25; found C 70.94, H 5.55, N 11.58.

*Ethyl N-2-cyano-1-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-3-ylformimidate (**13**)*

A mixture of 3-aminopyrrole-2-carbonitrile **9a** (0.015 mol), triethyl orthoformate (20 mL) and acetic anhydride (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. M. p. 150 – 152 °C (EtOH). Yield: 74 %. – IR (Nujol): ν = 2208 (CN), 1620 (C=N) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.32 (t, 3H, J = 7.5 Hz, CH_3), 3.82 (s, 3H, OCH_3), 4.33 (q, 2H, J = 7.5 Hz, CH_2), 7.15 (d, 2H, J = 9 Hz, Ar-H), 7.21 – 7.40 (m, 5H, Ar-H), 7.53 (d, 2H, J = 9 Hz, Ar-H), 8.19 (s, 1H, N=C*H*), 8.34 (s, 1H, 5-H). – MS (EI, 70 eV): *m/z* (%) = 345 (80) $[M]^+$. – $C_{21}H_{19}N_3O_2$ (345.39): calcd. C 73.03, H 5.54, N 12.17; found C 73.31, H 5.78, N 12.42.

*5-(4-Methoxyphenyl)-7-phenyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine (**14**)*

Method A: Amidine **13** (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 filtered off and crystallized from EtOH-DMF, 2 : 1.

Method B: A mixture of 3-amino-2-cyanopyrrole **9a** (0.01 mol), formamide (15 mL), *N,N*-dimethylformamide (5 mL), and formic acid (2 mL) was heated under reflux for 6 – 8 h. The reaction mixture was allowed to stand overnight at r. t. The solid obtained was filtered, washed with cold methanol, dried, and crystallized from EtOH-DMF, 2 : 1.

M. p. 268 – 270 °C. Yield: 71 %. – IR (Nujol): ν = 3458 – 3344 (NH_2) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.84 (s, 3H, OCH_3), 6.04 (bs, 2H, NH_2), 7.14 (d, 2H, J = 9 Hz, Ar-H), 7.21 (t, 1H, J = 8 Hz, Ar-H), 7.29 – 7.35 (m, 4H, Ar-H), 7.54 (d, 2H, J = 9 Hz, Ar-H), 8.29 (s, 1H, 2-H), 8.47 (s, 1H, 6-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 55.61 (O*C*H_3), 114.43 (C-7a), 114.97 (C-3′,5′), 122.51 (C-2″,6″), 126.42 (C-4″), 127.80 (C-2′,6′), 129.94 (C-1′), 131.76 (C-3″,5″), 137.76 (C-1″), 139.64 (C-6), 142.43 (C-7), 148.43 (C-4a), 150.86 (C-4), 152.63 (C-2), 159.91 (C-4′). – MS (EI, 70 eV): *m/z* (%) = 316 (48) $[M]^+$. – $C_{19}H_{16}N_4O$ (316.36): calcd. C 72.13, H 5.10, N 17.71; found C 72.34, H 5.45, N 17.98.

*N-(4-Chlorophenyl)-5-(4-methoxyphenyl)-7-phenyl-5H-pyrrolo[3,2-d]pyrimidin-4-amine (**16**)*

Method A: To a solution of amidine **13** (3.0 mmol) in methanol (20 mL) was added *p*-chloroaniline (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 (74 %).

Method B: To a solution of 4-chloropyrrolopyrmidines **18** (2.0 mmol) in methanol (20 mL) was added *p*-chloroaniline (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 (68 %).

M. p. 235 – 237 °C. Yield: 74 %. – IR (Nujol): ν = 3410 (NH) cm^{-1}. – ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ = 3.86 (s, 3H, OCH_3), 6.98 (s, H, NH), 7.01 – 7.08 (m, 1H, Ar-H), 7.16 (d, 2H, J = 9 Hz, Ar-H), 7.25 – 7.33 (m, 4H, Ar-H), 7.46 (d, 2H, J = 9 Hz, Ar-H), 7.61 (d, 2H, J = 9 Hz, Ar-H), 8.21 (d, 2H, J = 9 Hz, Ar-H), 8.51 (s, 1H, 2-H), 8.62 (s, 1H, 6-H). – ^{13}C NMR (75.4 MHz, [D_6]DMSO): δ = 55.71 (O*C*H_3), 114.11 (C-7a), 114.89 (C-3′,5′), 120.76 (C-2″,6″), 122.52 (C-b,f), 123.42 (C-4″), 128.10 (C-2′,6′), 128.81 (C-3″,5″), 129.21 (C-c,e), 129.84 (C-1′), 130.35 (C-d), 137.65 (C-a), 138.21 (C-1″), 140.10 (C-7), 140.62 (C-6), 147.43 (C-4), 148.87 (C-4a), 152.11 (C-2), 160.21 (C-4′). – MS (EI, 70 eV): *m/z* (%) = 426 (90) [M, ^{35}Cl]$^+$, 428 (23) [M, ^{37}Cl]$^+$. – $C_{25}H_{19}ClN_4O$ (426.90): calcd. C 70.34, H 4.49, N 13.12; found C 69.98, H 4.71, N 13.25.

*5-(4-Methoxyphenyl)-7-phenyl-3H-pyrrolo[3,2-d] pyrimidin-4(5H)-one (**17**)*

A mixture of 3-amino-2-cyanopyrrole **9a** (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). M. p. 301 – 304 °C. Yield: 66 %. – IR (Nujol): ν = 3340 (NH), 1690 (C=O) cm^{-1}. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 3.80 (s, 3H, OCH_3), 6.99 (d, 2H, J = 9 Hz, Ar-H), 7.15 – 7.35 (m, 5H, Ar-H), 7.64 (d, 2H, J = 9 Hz, Ar-H), 8.09 (s, 1H, 2-H), 8.14 (s, 1H, 6-H), 11.85 (s, 1H, NH). – MS (EI, 70 eV): *m/z* (%) = 317 (55) $[M]^+$. – $C_{19}H_{15}N_3O_2$ (317.34): calcd. C 71.91, H 4.76, N 13.24; found C 72.14, H 4.95, N 13.48.

*4-Chloro-5-(4-methoxyphenyl)-7-phenyl-5H-pyrrolo[3,2-d] pyrimidine (**18**)*

A mixture of pyrrolopyrimidin-4-one **17** (0.01 mol) and phosphorus oxychloride (25 mL) was refluxed for 9 h. After completion of the 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). M. p. 136 – 138 °C. Yield: 56 %. – ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 3.81 (s, 3H, OCH_3), 7.21 (d, 2H, J = 9 Hz, Ar-H), 7.35 – 7.38 (m, 2H, Ar-H), 7.50 – 7.54 (m, 3H, Ar-H), 7.56 (d, 2H, J = 9 Hz, Ar-H), 8.19 (s, 1H, 6-H), 8.35 (s, 1H, 2-H). – MS (EI, 70 eV): *m/z* (%) = 335 (46) [M, ^{35}Cl]$^+$, 337 (12) [M, ^{37}Cl]$^+$. – $C_{19}H_{14}ClN_3O$ (335.79): calcd. C 67.96, H 4.20, N 12.51; found C 67.66, H 4.35, N 12.19.

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