Synthesis of Some New Pyrazole and Pyrazolopyrimidine Derivatives [1]

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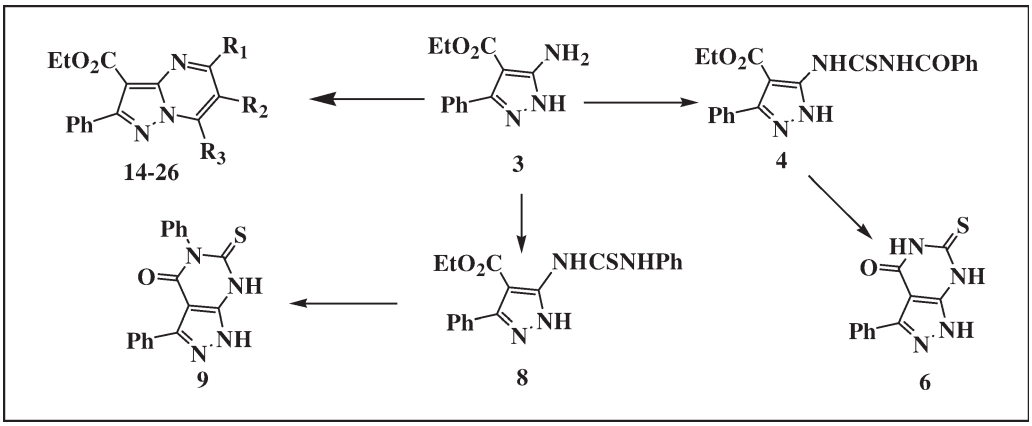

A series of pyrazolo [3,4-d] pyrimidine, pyrazolo [1,5-a] pyrimidine, and pyrazolyl triazoles have been prepared *via* reaction of ethyl 5-amino-3-phenylpyrazole-4-carboxylate with isothiocyanic esters, α,β-unsaturated nitriles, and some active methylene reagents.

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INTRODUCTION

In the past decade, we have been involved in a program aiming at the synthesis of new heterocyclic compounds that may possess biologically active properties to be used as potential biodegradable agrochemicals [2–5]. In continuation of our earlier interest in 3(5)-aminopyrazole, we report here an efficient synthesis of the *hitherto* unreported ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3** and its exploitation for the synthesis of some new fused pyrazole derivatives.

RESULTS AND DISCUSSION

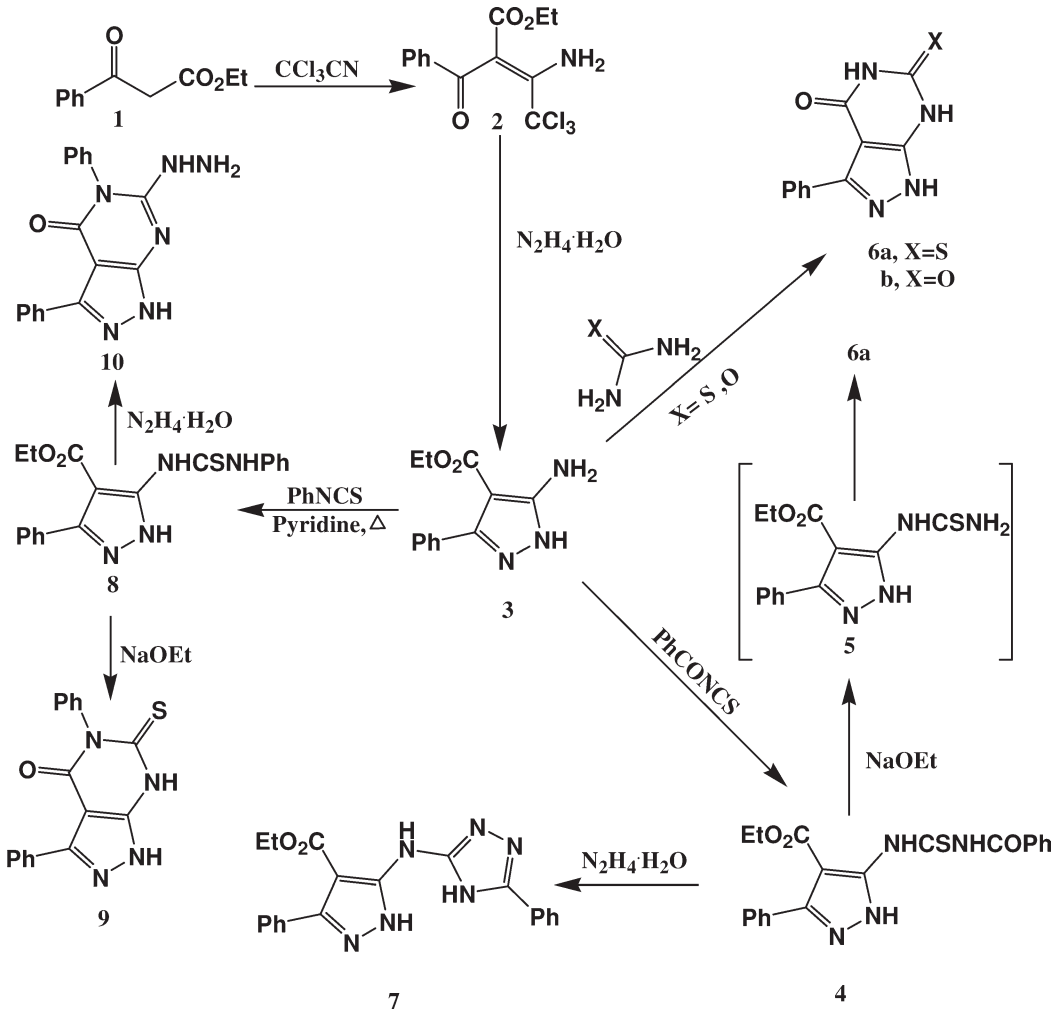
Thus, ethyl benzoylacetate **1** reacts with trichloroacetonitrile in ethanol catalyzed by sodium acetate to afford 1:1 adduct, which could be formulated as ethyl 3-amino-2-benzoyl-3-trichloromethyl acrylate derivative **2**. Structure **2** was assigned to this adduct on the basis of analytical and spectral data (cf. Experimental part). The reaction of **2** with hydrazine hydrate in refluxing pyridine afforded directly ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3**. The formation of **3** is assumed to occur *via* nucleophilic attack of hydrazine NH_2 on **2** with elimination of chloroform followed by the condensation of the hydrazide NH_2 with the benzoyl-carbonyl group with elimination of water. This cyclization was expected to occur with elimination of ethanol; however, all spectral evidence showed the presence of the ester function.

Thus, IR spectrum of the product showed that absorption bands at υ_{max} = 1651, 3415, and 3365 cm^{-1} attributable to carbonyl and amino groups. The ^1H NMR spectrum revealed a triplet at δ = 1.17–1.24 ppm (J = 10.6 Hz) and quartet at δ = 4.12–4.23 ppm (J = 10.6 Hz) characteristic for ethyl ester group, a singlet (2H, D_2O exchangeable) at δ = 6.21 ppm for amino group, a multiplet (5H) at δ = 7.42–7.66 ppm for aromatic protons, and a broad singlet (1H) at δ = 12.05 ppm for the pyrazole NH. Moreover, the mass spectrum of the reaction product showed a strong absorption at m/z = 231 (48%), which is compatible with the molecular formula $C_{12}H_{13}N_3O_2$ for compound **3**.

Aminopyrazoles are the most extensively utilized heterocyclic amines in heterocyclic synthesis due to their ready availability as well as their stability, which makes them useful precursors in dyes, pharmaceuticals, and agrochemical industries [6–13].

In conjunction with our interest in exploring the potential utility of functionally substituted pyrazoles

Scheme 1. Preparation of compounds **2**, **3**, **4**, **6a,b**, **7**, **8**, **9** and **10**.

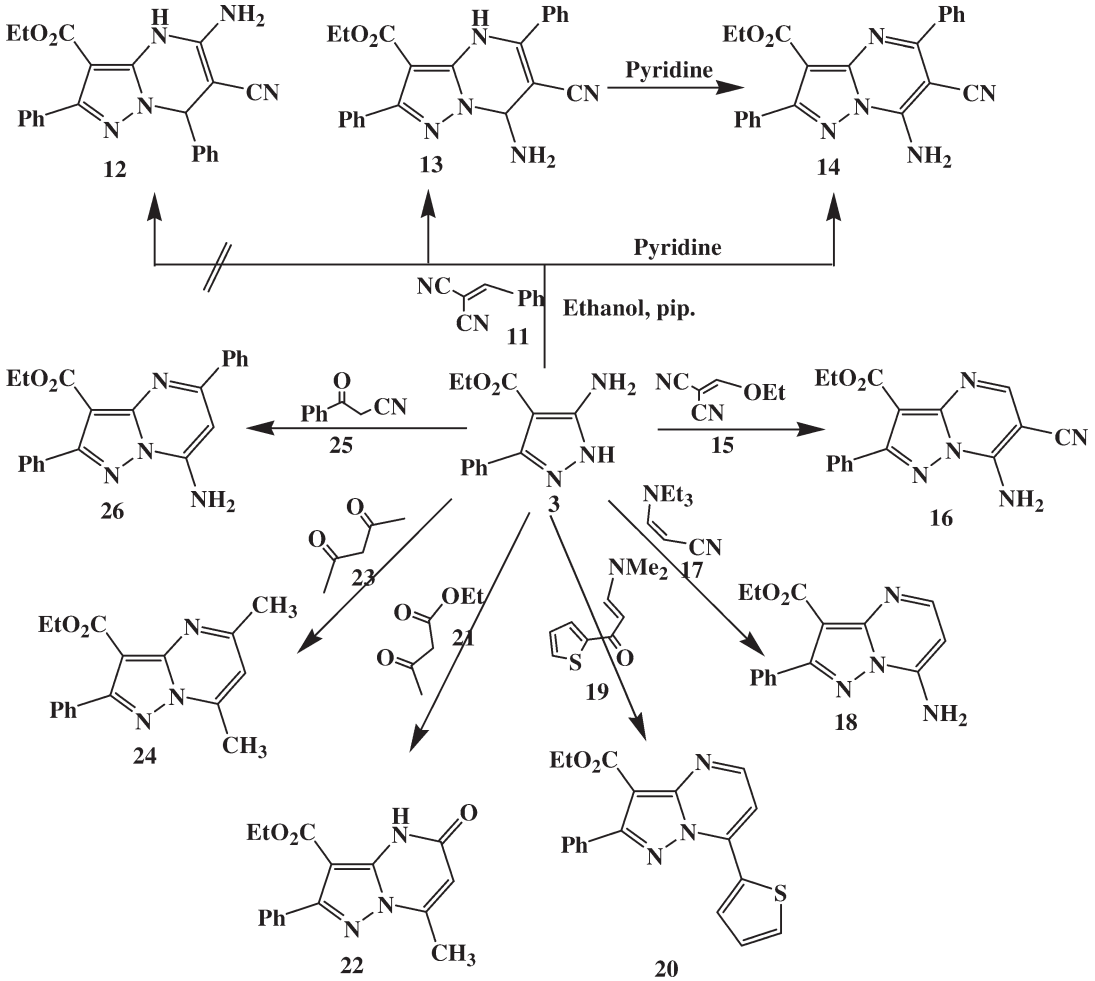


[14–16], we report here a simple and efficient synthesis of some new polyfunctionally substituted pyrazolopyrimidines of expected biological interest starting with our new pyrazole **3**.

Thus, ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-carboxylate **3** reacts with benzoyl isothiocyanate and phenyl isothiocyanate to afford the 1:1 adducts **4** and **8**, respectively, *via* electrophilic attack at the amino group, which was considered most likely for these adducts based on their stability under the conditions reported to effect decomposition of *N*-thiocarbamoyl pyrazoles [16–18]. Attempts to effect cyclization of both reaction products **4** and **8** by boiling in ethanolic sodium ethoxide has resulted in the formation of pyrazolo[3,4-d]pyrimidines **6a** and **9**, respectively. Structures **6a** and **9** are identified on the basis of analytical and spectral data, where the ^{1}H NMR spectrum of **6a** revealed the presence of a multiplet at δ = 7.45–8.15 ppm (5H) for aromatic protons and three singlets at δ = 11.82, 12.99, and 13.88 ppm for NH-pyrazole and two NH-pyrimidine protons. The formation of **6a** from **4** seemed to proceed *via* alcoholysis with loss of the benzoyl moiety and the formation of the nonisolable intermediate **5**, which undergoes cyclization through ethanol elimination to give **6a** (Scheme 1). An authentic sample of **6a** has been obtained from the reaction of the pyrazole **3** with thiourea by fusion in an oil bath at 120°C (The same melting point, mixed melting point, and same analytical and spectral analyses). The loss of the benzoyl moiety in similar reaction is reported in [16–18].

The thiourea derivatives **4** and **8** reacted with hydrazine hydrate and afforded products for which structures **7** and **10** were assigned on the basis of analytical and spectral analyses, where the ^{1}H NMR spectrum of **7** showed the presence of a triplet at δ = 1.13 ppm (J = 7.2 Hz), a quartet at δ = 4.15 ppm (J = 7.2 Hz), a

Scheme 2. Preparation of compounds **13**, **14**, **16**, **18**, **20**, **22**, **24** and **26**.



multiplet at δ = 7.45–8.15 ppm for 10 protons (aromatic protons), a singlet at δ = 9.20 ppm for Pyrazole-NH, and two singlets at δ = 11.90 and 13.05 ppm for both exocyclic NH and triazole-NH protons.

On the other hand, the ^{1}H NMR of **10** revealed the presence of a singlet at δ = 5.56 ppm for the amino group protons, a multiplet at δ = 7.11–8.39 ppm integrated for 10H (2-Ph protons), a singlet at δ = 9.47 ppm for pyrazole-NH, and a singlet at δ = 13.18 ppm for hydrazine-NH. The ^{13}C NMR spectrum of **10** revealed signals at 102.64 (C-4 pyrazolopyrimidine), 121.62, 123.60, 127.54, 128.18, and 128.62 (CH aromatic), 132.77 (C-9 pyrazolopyrimidine), 136.28, 138.25, and 147.12 (CH aromatic), 150.91 (C-3 pyrazolopyrimidine), 153.76 (C-7 pyrazolopyrimidine), and 157.59 (C-6 pyrazolopyrimidine) (CO).

The pyrazolo[3,4-*d*]pyrimidine-4,6-dione analogue **6b** has been obtained *via* reaction of the 5-aminopyrazole **3** with urea on fusion in oil bath at 120°C. Structure **6b** was assigned on the basis of elemental analysis and spectral data (cf. Experimental section).

Pyrazolo[1,5-*a*]pyrimidines are important due to their ability to inhibit 3′,5′-cyclic phosphodiestrase and their cardiotropic properties [19,20]. Moreover, the reported activities of pyrazolo[1,5-*a*]pyrimidines as antipyretics, anti-inflammatory, anticancer, and antischistosomal agents [21–23] prompted us to prepare some of their new derivatives *via* reacting our new 5-aminopyrazole derivative **3** with some α,β-unsaturated nitriles and active methylene reagents.

Thus, ethyl 5-amino-3-phenyl-1*H*-pyrazole-4-caboxylate **3** reacts with the cinnamonitrile derivative **11** in refluxing ethanol with few drops of piperidine as a catalyst to afford products for which structures **12** or **13** seemed possible (cf. Scheme 2).

The spectral data of the reaction products suggested structure **13** to be assigned to this product rather than **12** (cf. Experimental section). Compound **13** was transformed into the fully aromatic pyrazolo[1,5-*a*]pyrimidine derivative **14** on reflux in pyridine. When the reaction of **3** with **11** was carried out in refluxing pyridine compound **14** was also obtained. The identity of the two

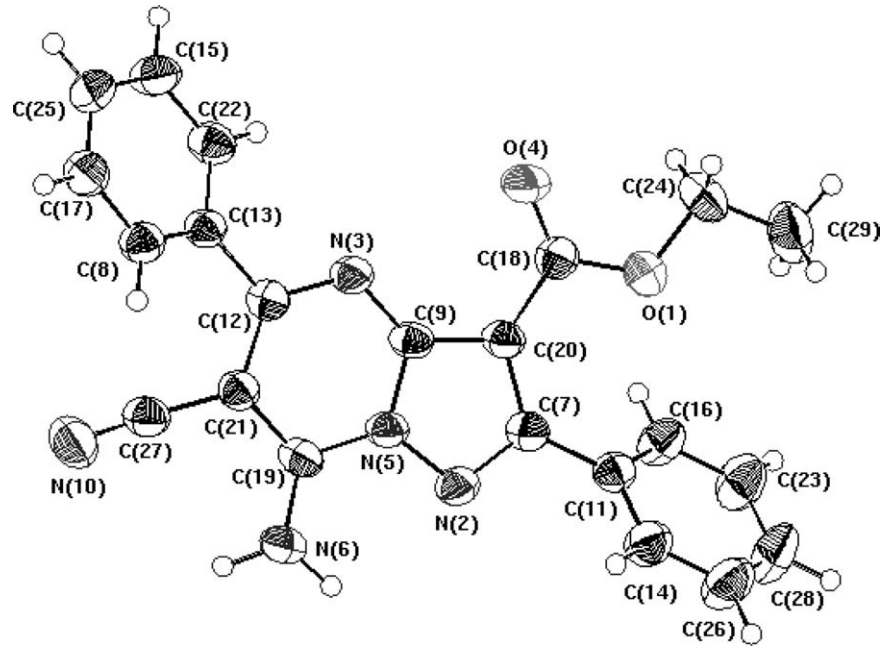


Figure 1. Single crystal X-ray structure of compound **14** [24–26].

products was inferred from melting points and spectral data. Structure **14** was assigned on the basis of the ^{13}C NMR and ^{1}H NMR spectra which revealed the disappearance of the pyrimidine-4-H signal and presence of a singlet at $\delta = 6.83$ ppm integrated for two protons (NH_2 protons) in addition to the other expected signals for aromatic and ethyl ester protons (cf. Experimental). The formation of **14** from **13** apparently takes place *via* auto-oxidation under the reaction conditions. Similar reactions have been reported [22,23].Structure **14** was unambiguously confirmed on the basis of the single crystal X-ray analysis [24–26] (cf. Fig. 1).

The aminopyrazole **3** reacted with ethoxy-methylene malononitrile **15** and afforded a product for which structure **16** is established based on analytical and spectral analyses.

On the other hand, when the 5-aminopyrazole **3** was condensed with both the enaminonitrile **17** and the enaminone **19**, it yielded the pyrazolo[1,5-*a*]pyrimidine derivatives **18** and **20**, respectively.

Structure **18** could be established on the basis of spectral analysis where the ^{1}H NMR spectrum revealed the amino group as a singlet at $\delta = 9.94$ ppm and the appearance of two doublets at $\delta = 6.56$ ppm ($J = 7.2$ Hz) and $\delta = 8.26$ ppm ($J = 7.2$ Hz) which may be attributed to H-5 and H-6.

5-Aminopyrazole-4-carboxylate **3** was also condensed with ethyl acetoacetate **21**, acetylacetone **23**, and benzoylacetonitrile **25** by fusion on oil bath at 100–120°C to yield products for which structures **22**, **24**, and **26** have been established, respectively, on the basis of analytical and spectral analyses. The IR spectrum of compound **22** revealed an absorption band at $\nu_{max} = 1712$ cm^{-1} for carbonyl ester and another band at $\nu_{max} = 1662$ cm^{-1} for amide carbonyl group.

The ^{1}H NMR spectrum of **24** showed two singlets at $\delta = 2.70$ and 2.80 ppm for the two methyl groups and a singlet at $\delta = 6.75$ ppm for pyrimidine-CH proton, beside the other expected signals for aromatic and ethyl ester protons. The formation of **26** apparently proceeds in a manner similar to the addition of the cinnamonitrile **11** shown above (cf. Scheme 2, Fig. 1, Experimental).

EXPERIMENTAL

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-Vector 22 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 MHz and 75 MHz, respectively, on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS - QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Micro analytical Center, Cairo University. The single crystal structure [24–26] was determined by X-ray unit at the National Research Center, Dokki, Giza, A. R. Egypt.

3-Amino-2-benzoyl-4,4,4-trichloro-butyric acid ethyl ester (2). To a solution of ethyl benzoylacetate **1** (1.92 g, 10 mmol) in absolute ethanol (50 mL) containing sodium acetate,

trichloroacetonitrile (1.44 g, 10 mmol) was added. Stirring lasted overnight at room temperature then the reaction mixture was poured into cold water. The resulting product obtained was filtered off, dried, and recrystallized from ethanol. White crystal (yield 80%), m.p. 107°C. ν_{max} cm^{-1} = 3375, 3240 (NH_2), 1674, 1645 (CO). MS: *m/z* 336 (M^+). Anal. Calcd. for $C_{13}H_{12}Cl_3NO_3$ (336.05): C, 46.38; H, 3.59; N, 4.16; Cl, 31.59%. Found: C, 46.31; H, 3.52; N, 4.11; Cl, 31.53%.

5-Amino-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (3). To a suspension of **2** (3.36 g, 10 mmol) in ethanol was added the equivalent amount of hydrazine hydrate (0.50 mL, 10 mmol) and triethylamine as catalyst. The reaction mixture was refluxed for 5 h and then concentrated in *vacuo*. The solid product obtained upon cooling was isolated by filtration and recrystallized from a mixture of ethanol/dioxane. White crystal (yield 50%). m.p. 172°C. ν_{max} cm^{-1} = 3415, 3365 (NH_2), 3245, 1651 (CO). MS: *m/z* 231 (M^+). δ_H = 1.17 (t, 3H, *J* = 10.6 Hz, CH_3), 4.12 (q, 2H, *J* = 10.6 Hz, CH_2), 6.21 (s, 2H, NH_2), 7.42–7.66 (m, 5H, Ar-H), 12.04 (s, 1H, NH-pyrazole). Anal. Calcd. for $C_{12}H_{13}N_3O_2$ (231.26): C, 62.32; H, 5.66; N, 18.17%. Found: C, 62.25; H, 5.60; N, 18.08%.

5-(3-Benzoyl-thioureido)-3-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester (4). A solution of **3** (2.31 g, 10 mmol) and benzoyl isothiocyanate (1.63 g, 10 mmol) in dry acetone (50 mL) were refluxed for 5 h. The reaction mixture was evaporated under vacuo. The resulting solid was collected by filtration and crystallized from ethanol. White crystal (yield 50%), m.p. 158°C. υ_{max} cm^{-1} = 3425, 3193 (NH), 1720, 1681 (CO). MS: *m/z* 394 (M^+). Anal. Calcd. for $C_{20}H_{18}N_4O_3S$ (394.45): C, 60.89; H, 4.59; N, 14.20; S, 8.12%. Found: C, 60.81; H, 4.53; N, 14.13; S, 8.08%.

Synthesis of (6a). Method 1. Compound **4** (10 mmol) was treated with ethanolic sodium ethoxide (0.23 g sodium in 50 mL ethanol), the reaction mixture was refluxed for 3 h and allowed to cool then poured into cold water and neutralized with dil. HCl. The resulting product was collected by filtration and crystallized from ethanol to afford **6a** in 72% yield.

Synthesis of (6a, b). Compound **3** (2.31 g, 10 mmol) was treated with thiourea (0.76 g, 10 mmol) or urea (0.60 g, 10 mmol) and the reaction mixture was heated in oil bath at 100–120°C for 2 h. The mixture was allowed to cool at room temperature. The formed solid product was crystallized from ethanol/dioxane to afford **6a** and **6b**, respectively.

3-Phenyl-6-thioxo-1,5,6,7-tetrahydro-pyrazolo [3,4-d] pyrimidin-4-one (6a). Pale brown crystal (yield 65%), m.p > 300°C. υ_{max} cm^{-1} = 3215, 3120 (NH), 1593 (CO). MS: *m/z* 244 (M^+). δ_H = 7.50–8.15 (m, 5H, Ar-H), 11.82 (s, 1H, NH-pyrazole), 12.99 (s, 1H, NH-pyrimidine), 13.88 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{11}H_8N_4OS$ (244.27): C, 54.09; H, 3.30; N, 22.93; S, 13.34%. Found: C, 54.02; H, 3.27; N, 22.85; S, 13.29%.

3-Phenyl-1,7-dihydro-pyrazolo [3,4-d] pyrimidine-4,6-dione (6b). Pale yellow crystal (yield 60%), m.p > 300°C. υ_{max} cm^{-1} = 3430, 3223 (NH), 1730, 1640 (CO). MS: *m/z* 228 (M^+). δ_H = 7.43–8.14 (m, 5H, Ar-H), 10.65 (s, 1H, NH-pyrazole), 11.35 (s, 1H, NH-pyrimidine), 13.55 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{11}H_8N_4O_2$ (228.21): C, 57.89; H, 3.53; N, 24.55%. Found: C, 57.81; H, 3.48; N, 24.49%.

3-Phenyl-5-(3-phenyl-thioureido)-1*H*-pyrazole-4-carboxylic acid ethyl ester (8). Phenyliso-thiocyanate (1.35 g, 10 mmol) was added to a solution of **3** (2.31 g, 10 mmol) in pyridine and were refluxed for 3 h and then allowed to cool at room temperature. The reaction mixture was poured into ice cold water and neutralized with dil. HCl. The resulting solid was collected by filtration and crystallized from ethanol. The product is identified as **8**. Pale yellow crystal (yield 50%), m.p. 218°C. υ_{max} cm^{-1} = 3355, 3210 (NH), 1654 (CO). MS: *m/z* 366 (M^+). Anal. Calcd. for $C_{19}H_{18}N_4O_2S$ (366.49): C, 62.26; H, 4.95; N, 15.28; S, 8.74%. Found: C, 62.21; H, 4.89; N, 15.23; S, 8.68%.

3,5-Diphenyl-6-thioxo-1,5,6,7-tetrahydro-pyrazolo [3,4-*d*] pyrimidin-4-one (9). Compound **8** (10 mmol) was treated with ethanolic sodium ethoxide solution (0.23 g sodium in 50 mL absolute ethanol). The reaction mixture was heated under reflux for 3 h, allowed to cool, then poured onto ice cold water and neutralized with dil. HCl. The resulting solid product is collected by filtration and crystallized from ethanol and identified as **9**. White crystal (yield 55%), m.p. > 300°C. υ_{max} cm^{-1} = 3153, 3056 (NH), 1696 (CO). MS: *m/z* 320 (M^+). Anal. Calcd. for $C_{17}H_{12}N_4OS$ (320.37): C, 63.73; H, 3.77; N, 17.48; S, 10.00%. Found: C, 63.64; H, 3.69; N, 17.40; S, 9.92%.

General method for preparation of (7) and (10). Compound **4** or **8** (10 mmol) reacted with hydrazine hydrate (0.50 mL, 10 mmol) in pyridine (25 mL) and heated under reflux for 3 h, then allowed to cool at room temperature. The reaction mixtures were poured onto ice cold water and neutralized with dilute HCl. The resulting solids were collected by filtration and crystallized from ethanol.

3-Phenyl-5-(5-phenyl-4H-[1,2,4]triazol-3-ylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (7). Pale brown crystal (yield 70%), m.p. > 300°C. υ_{max} cm^{-1} = 3325, 3175, 3150 (NH), 1676 (CO). MS: *m/z* 374 (M^+). δ_H = 1.13(t, 3H, *J* = 7.2 Hz, CH_3), 4.15 (q, 2H, *J* = 7.2 Hz, CH_2), 7.45–8.15 (m, 10H, 3Ar-H), 9.20 (s, 1H, NH-pyrazole). 11.90 (s, 1H, NH), 13.05 (s, 1H, NH-triazole). Anal. Calcd. for $C_{20}H_{18}N_6O_2$ (374.41): C, 64.42; H, 4.84; N, 22.44%. Found: C, 64.38; H, 4.80; N, 22.37%.

6-Hydrazide-3,5-diphenyl-1,5-dihydro-pyrazolo [3,4-d] pyrimidin-4-one (10). White crystal (yield 50%), m.p. 295°C. υ_{max} cm^{-1} = 3350, 3235 (NH_2), 3150 (NH). MS: *m/z* 318 (M^+). δ_H = 5.56 (s, 2H, NH_2), 7.11–8.39 (m, 10H, 2Ar-H), 9.47 (s, 1H, NH-pyrazole), 13.18 (s, 1H, NH-hydrazide). δ_C = 102.64 (C-4 pyrazolopyrimidine), 121.62, 123.60, 127.54, 128.18, and 128.62 (CH aromatic), 132.77 (C-9 pyrazolopyrimidine), 136.28, 138.25, and 147.12 (CH aromatic), 150.91 (C-3 pyrazolopyrimidine), 153.76 (C-7 pyrazolopyrimidine), 157.59 (C-5 pyrazolopyrimidine) (CO). Anal. Calcd. for $C_{17}H_{14}N_6O$ (318.34): C, 64.14; H, 4.43; N, 26.39%. Found: C, 64.09; H, 4.38; N, 26.31%.

7-Amino-6-cyano-2,5-diphenyl-4,7-dihydro-pyrazolo[1,5-*a*] pyrimidine-3-carboxylic acid ethyl ester (13). Compounds **11** (1.54 g, 10 mmol) were refluxed for 3 h with compound **3** (2.31 g, 10 mmol) in ethanol (50 mL) and few drops of piperidine as catalyst. The reaction mixture was then poured into ice-cold water and neutralized with dilute HCl. The resulting solid product was collected by filtration and crystallized from ethanol. White crystal (yield 65%), m.p. 220°C. υ_{max} cm^{-1} = 3446, 3400 (NH_2), 3315 (NH), 2190 (CN), 1686 (CO). MS: *m/z* 385 (M^+). δ_H ($CDCl_3$) = 1.18 (t, 3H, *J* = 7.2 Hz, CH_3), 4.17 (q, 2H, *J* = 7.2 Hz, CH_2), 5.48 (s, 3H, NH_2, CH-pyrimidine), 6.72 (s, 1H, NH-pyrimidine), 7.39–7.70 (m, 10H, 2Ar-H). Anal. Calcd. for $C_{22}H_{19}N_5O_2$ (385.43): C, 68.55; H, 4.96; N, 18.17%. Found: C, 68.50; H, 4.92; N, 18.08%.

7-Amino-6-cyanio-2,5-diphenyl-pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (14). Compound **13** (3.85 g, 10 mmol) was dissolved in 25 mL pyridine (or 25 mL DMF) and heated under reflux for 3 h, then evaporated in vacuo and diluted with cold water (50 mL) then treated with few drops of dil. HCl. The resulting solid product is filtered off, washed well with cold water, and crystallized from ethanol/dioxane mixture. The solid product is identified as **14**. Brown crystal (yield 55%), m.p. 208°C. υ_{max} cm^{-1} = 3415, 3365 (NH_2), 2219 (CN), 1685 (CO). MS: *m*/*z* 382 (M^+-1). δ_H = 1.31 (t, 3H, *J* = 7.2 Hz, CH_3), 4.34 (q, 2H, *J* = 7.2 Hz, CH_2), 6.83 (s, 2H, NH_2) 7.48–8.07 (m, 10H, 2Ar-H). δ_C = 14.11 (CH_3 ester), 60.55 (CH_2 ester), 75.27 (C-7 pyrazolopyrimidine), 106.23 (C-8 pyrazolopyrimidine), 115.41 (CN), 127.95, 128.59, 128.93, 129.59, 129.64, 131.07, 131.83, and 136.54 (CH aromatic), 148.69 (C-6 pyrazolopyrimidine), 150.55 (C-2 pyrazolopyrimidine), 159.99 (C-4 pyrazolopyrimidine), 160.79 (C-3 pyrazolopyrimidine), 162.69 (CO). Anal. Calcd. for $C_{22}H_{17}N_5O_2$ (383.41): C, 68.91; H, 4.46; N, 18.26%. Found: C, 68.87; H, 4.37; N, 18.19%.

X-ray crystallographic data using *SIR*92 [25] program to solve structure: Yellow crystals, $C_{22}H_{17}N_5O_2$ (M_r = 383.411 $gmol^{-1}$), orthorhombic prismatic, space group *Pna*-2(1), *a* = 8.8207(2) Å, *b* = 16.6408(4) Å, *c* = 25.7103(9) Å, α[°] = 90.00, β[°] = 90.00, γ[°] = 90.00; *V*[$Å^3$] = 3773.8(2). *Z* = 8, D_x = 1.350 Mgm^{-3}, μ(Mo K_α) = 0.09 mm^{-1}; Fine-focus sealed tube. Data were collected using KappaCCD. *T*[K] = 298, with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å), θ = 2.910–25.028°. Measured reflections 6613, Total independent reflections are 3780 were counted with observed reflections 1830. R_{int} = 0.031. *R*(all) = 0.112, *R*(gt) = 0.042, wR(ref) = 0.078, and wR(all) = 0.097.

General procedure for preparation of compounds (16), (18), and (20). Compound **3** (2.31 g, 10 mmol) was added to a solution of **15**, **17**, or **19** (10 mmol) in pyridine (25 mL) and refluxed for 3 h. The reaction mixtures were evaporated under vacuo then poured onto ice cold water, and neutralized with diluted HCl. The resulting solids were collected by filtration and crystallized from dioxane/ethanol and identified as **16**, **18**, and **20**, respectively.

7-Amino-6-cyano-2-phenyl-pyrazolo [1,5-a]pyrimidine-3-carboxylic acid ethyl ester (16). Brown crystal (yield 60%), m.p. 282°C. υ_{max} cm^{-1} = 3406, 3220 (NH_2), 2221(CN), 1697, (CO). MS: *m*/*z* 307 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5O_2$ (307.31): C, 62.53; H, 4.26; N, 22.79%. Found: C, 62.45; H, 4.19; N, 22.69%.

7-Amino-2-phenyl-pyrazolo [1,5-a] pyrimidine-3-carboxylic acid ethyl ester (18). White crystal (yield 70%), m.p. 204°C. υ_{max} cm^{-1} = 3427, 3372 (NH_2), 1671 (CO). MS: *m*/*z* 282 (M^+). δ_H = 1.21 (t, 3H, *J* = 7.2 Hz, CH_3), 4.28 (q, 2H, *J* = 7.2 Hz, CH_2), 6.56 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-5), 7.50–7.81 (m, 5H, Ar-H), 8.26 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-6), 9.94 (s, 1H, NH_2). Anal. Calcd. for $C_{15}H_{14}N_4O_2$ (282.31): C, 63.81; H, 4.99; N, 19.84%. Found: C, 63.72; H, 4.91; N, 19.79%.

2-Phenyl-7-thiophen-2-yl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (20). Pale yellow crystal (yield 65%), m.p. 159°C. υ_{max} cm^{-1} = 3062 (CH-Aromatic), 1697(CO). MS: *m*/*z* 349 (M^+). δ_H = 1.21(t, 3H, *J* = 6.9 Hz, CH_3), 4.27(q, 2H, *J* = 6.9 Hz, CH_2), 7.39–7.90 (m, 6H, Ar-H, thiophene-H-2), 7.95 (d, 1H, *J* = 3.9 Hz, thiophene-H-3), 8.14 (d, 1H, *J* = 3.9 Hz, thiophene-H-1), 8.57 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-6), 8.80 (d, 1H, *J* = 7.2 Hz, pyrazolopyrimidine-H-5). Anal. Calcd. for $C_{19}H_{15}N_3O_2S$ (349.41): C, 65.31; H, 4.33; N, 12.03; S, 9.18%. Found: C, 65.22; H, 4.38; N, 11.92; S, 9.05%.

General procedure for preparation of compounds (22), (24), and (26). Compound **3** (2.31 g, 10 mmol) and 10 mmol of either ethyl acetoacetate **21**, acetylacetone **23**, or benzoylacetonitrile **25** were reacted under thermal conditions in oil bath at 100–120°C for 2 h. The formed solid products were washed well with ethanol and crystallized from ethanol/dioxane to afford **22**, **24**, and **26**, respectively.

7-Methyl-5-oxo-2-phenyl-4,5-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester (22). White crystal (yield 70%), m.p 185°C. υ_{max} cm^{-1} = 3200 (NH), 1712, 1662 (CO). MS: *m*/*z* 299 (M^++2). δ_H = 1.17(t, 3H, *J* = 7.2 Hz, CH_3), 3.30 (s, 3H, CH_3), 4.22 (q, 2H, *J* = 7.2 Hz, CH_2), 5.87 (s, 1H, pyrimidine-H), 7.43–7.71 (m, 5H, Ar-H), 11.54 (s, 1H, NH-pyrimidine). Anal. Calcd. for $C_{16}H_{15}N_3O_3$ (297.32): C, 64.63; H, 5.08; N, 14.13%. Found: C, 64.56; H, 4.98; N, 14.02%.

5,7-Dimethy-2-phenyl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid ethyl ester (24). Yellow crystal (yield 50%), m.p. 124°C. υ_{max} cm^{-1} = 3060 (CH-Aromatic), 1678 (CO). MS: *m*/*z* 295 (M^+). δ_H = 1.25 (t, 3H, *J* = 6.9 Hz, CH_3), 2.70 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.31 (q, 2H, *J* = 6.9 Hz, CH_2), 6.75 (s, 1H, pyrimidine-H) 7.44–7.77 (m, 5H, Ar-H). Anal. Calcd. for $C_{17}H_{17}N_3O_2$ (295.34): C, 69.13; H, 5.80; N, 14.22%. Found: C, 69.05; H, 5.75; N, 14.17%.

7-Amino-2,5-diphenyl-pyrazolo[1,5-a] pyrimidine-3-carboxylic acid ethyl ester (26). Yellow crystal (yield 55%), m.p. > 300°C. υ_{max} cm^{-1} = 3305, 3170 (NH_2), 1654 (CO). MS: *m*/*z* 358 (M^+). Anal. Calcd. for $C_{21}H_{18}N_4O_2$ (358.40): C, 70.37; H, 5.06; N, 15.63%. Found: C, 70.29; H, 4.97; N, 15.55%.

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[24] Crystallographic data (excluding structure factors) for the structure **8a** reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-755428. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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