Pyrazolo[1,5-*a*]Pyrimidine Derivative as Precursor for Some Novel Pyrazolo[1,5-*a*]Pyrimidines and Tetraheterocyclic Compounds

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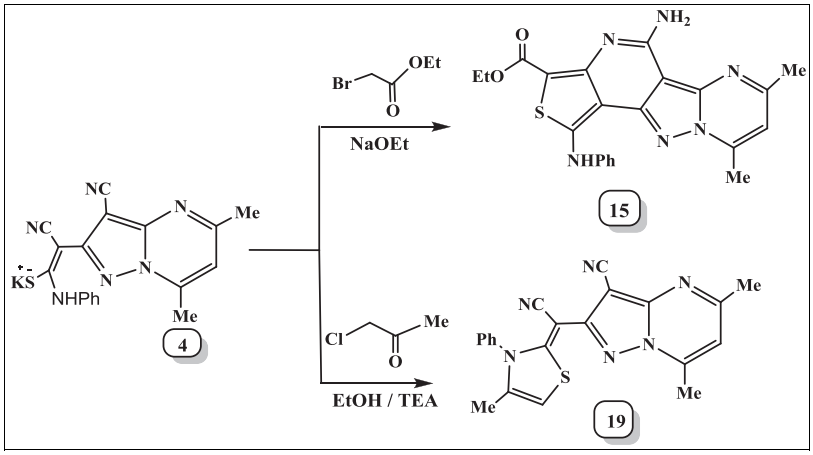
Additional Supporting Information may be found in the online version of this article.
Received August 21, 2015
DOI 10.1002/jhet.2590
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



The 2-(cyanomethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **3** reacted with phenyl isothiocyanate to afford the respective thioanilide derivative **4** that is a novel compound that has been unreported hitherto. The latter was used as a precursor to synthesize several novel polyheterocyclic compounds **9**, **12**, **15**, and **19**. Treatment of the enamine derivative of compound **3** with each of hydrazine hydrate and hydroxylamine hydrochloride yielded the tetraheterocyclic compounds **22** and **23**, respectively. The structures of all the newly synthesized compounds were confirmed on basis of their elemental, spectral data, and plausible mechanism has been postulated to account for their formation. X-ray crystallography was carried out as a further evidence for the structure of the isolated product **19**.

J. Heterocyclic Chem., **00,** 00 (2016).

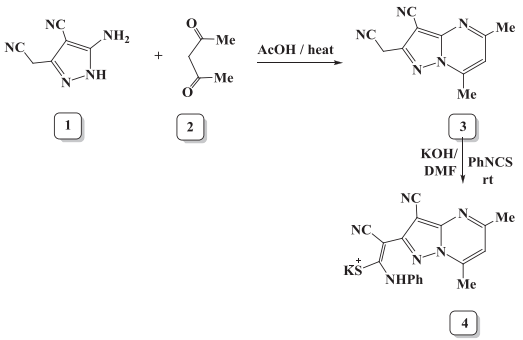
INTRODUCTION

Pyrazolo[1,5-*a*]pyrimidine derivatives are considered as important class of heterocyclic compounds, which have a broad spectrum of pharmacological and biological activities such as analgesic [1], antischistosomal [2], neuroleptic [3], antimicrobial [4], and tuberculostatic [5], in addition, act as potent inhibitors of Pim-1 kinase [6]. Also, compounds of this class are considered as antianxiety agents [7] and as an agent for the treatment of sleep disorders [8]. Moreover, pyrazolo[1,5-*a*]pyrimidines have an important synthetic value in the preparation of drugs with anticancer activities [9–11]. In continuation of our interest in synthesis of some new bioactive heterocyclic compounds [12–18], we report herein the preparation of polyheterocycles from pyrazolo[1,5-*a*]pyrimidine derivative. 2-(Cyanomethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile seemed to be a good candidate to fulfill this objective via its thioanilide derivative that has been unreported hitherto. Also, we evaluated the antimicrobial activity of some representative examples of the newly synthesized compounds.

RESULTS AND DISCUSSION

The required starting 2-(cyanomethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **3** was prepared by the reaction of 5-amino-3-cyanomethyl-1*H*-pyrazole-4-carbonitrile **1** and acetylacetone **2** under reflux in glacial acetic acid. The reaction of compound **3** with phenyl isothiocyanate in dimethylformamide in the presence of potassium hydroxide afforded yellow crystals of isolable product **4** (Scheme 1). The structure of **4** was confirmed by its elemental analyses and spectroscopic data (IR and ^{1}H NMR). The IR spectrum of this product showed absorption bands at ν_{max} 2215, 2171 cm^{-1} due to the cyano groups. The ^{1}H NMR spectrum of compound **4** revealed the presence of three singlet signals assigned to two methyl and pyrimidine protons at $\delta = 2.67$, 2.89, and 6.91 ppm, respectively. In addition, a D_2O exchangeable signal appeared at $\delta = 11.75$ ppm corresponding to the NH proton. Its ^{13}C NMR spectrum showed signals at $\delta = 16.9$ and 24.3 ppm assignable to two methyl carbons and a signal at $\delta = 161.3$ ppm corresponding to vinylic carbon, besides the expected signals for cyano and aromatic carbons. The

Scheme 1

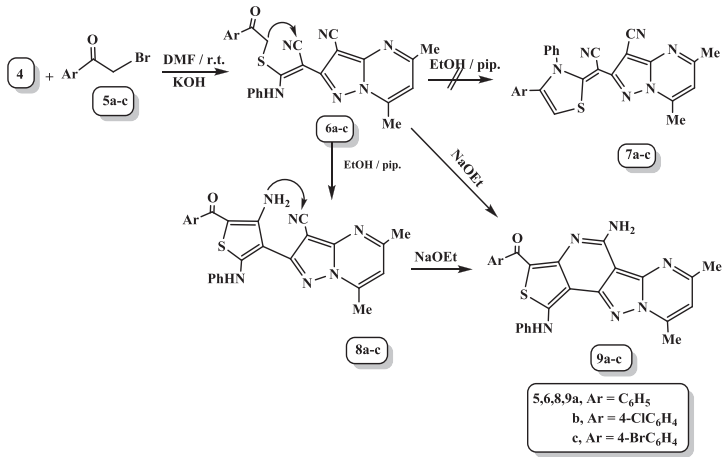


spectral data together with the elemental analysis are in agreement with the structure **4** (Experimental section).

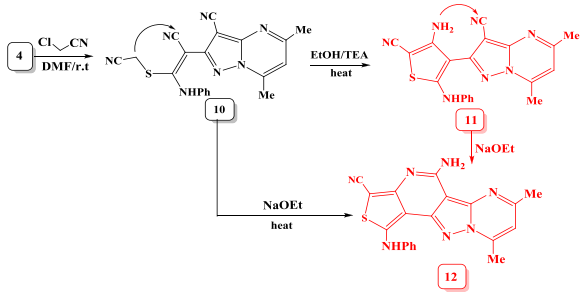
The reaction of the potassium salt **4** was exploited to synthesize some novel tetraheterocyclic compounds. Therefore, compound **4** reacted with ω-bromoacetophenone derivatives **5a–c** in dimethylformamide at room temperature, to afford a single product in each case (Scheme 2). The structures of the isolated products **6a–c** were deduced from elemental analysis and spectral data. For example, the IR spectrum of **6a** showed absorption bands at ν_{max} 2211 and 1674 cm^{-1} due to the two cyano and carbonyl groups, respectively. Its ^{1}H NMR spectrum revealed three singlet signals at $\delta = 2.60$, 2.76, and 6.55 ppm, assigned to the two methyl and CH_2 protons, in addition to, the other expected signals for aromatic and pyrimidine protons. The ^{13}C NMR spectrum for compound **6a** showed signals at $\delta = 17.1$, 23.8, 40, 117, and 118 ppm corresponding to two methyl, two cyano, and methylene carbons, respectively. Mass spectrum as well as elemental analysis was in agreement with the proposed structure **6a**. On the other hand, refluxing **6a–c** in absolute ethanol containing few drops of piperidine as a basic catalyst afforded a single product in each case. The structure of the isolated products **8a–c** was established by their elemental analysis and spectral data. The IR spectrum of **8a** taken as a typical example of the prepared series showed absorption bands at ν_{max} 3319, 3144, and 2218 cm^{-1} corresponding to the NH_2, NH, and CN groups, respectively, in addition to an absorption band at ν_{max} 1620 cm^{-1} corresponding to the carbonyl group. Its ^{1}H NMR spectrum revealed a D_2O-exchangeable signal at $\delta = 7.96$ ppm attributable to NH protons, besides the other expected signals for amino, aromatic, and pyrimidine protons. Elemental analysis was also in agreement with structure **8a**. The compounds **8a–c** were refluxed in sodium ethoxide solution-afforded isolated products **9a–c**. The structure of compounds **9a–c** was established by their elemental analysis and spectral data. The IR spectrum of compound **9a** revealed the disappearance of nitrile absorption bands near ν_{max} 2200 and instead showed an absorption bands at ν_{max} 3309 and 3050 cm^{-1} due to the amino and imino groups, in addition to an absorption band at ν_{max} 1633 cm^{-1}corresponding to the carbonyl group. Its ^{1}H NMR spectrum revealed a D_2O-exchangeable signals at $\delta = 10.06$ ppm attributable to NH proton and a multiplet signal at $\delta = 7.22$–7.79 ppm corresponding to amino and aromatic protons. The ^{13}C NMR spectrum of **9a** was free from signals corresponding to cyano carbons at $\delta = 117$ and 118 ppm. Elemental analysis was also in agreement with the proposed structure **9a** (Experimental section).

Similarly, the reaction of compound **4** with chloroacetonitrile in dimethylformamide at room temperature afforded a single product identified as *S*-alkyl derivative **10** (Scheme 3) based on the elemental and spectral analyses of the isolated product (Experimental section). Refluxing compound **10** in absolute ethanol in the presence of few drops of triethylamine afforded a single product identified as fused thiophene derivative **11** based on the elemental analyses and spectral data (Scheme 3 and Experimental section). The latter compound was refluxed in sodium ethoxide solution afforded the tetraheterocyclic

Scheme 2



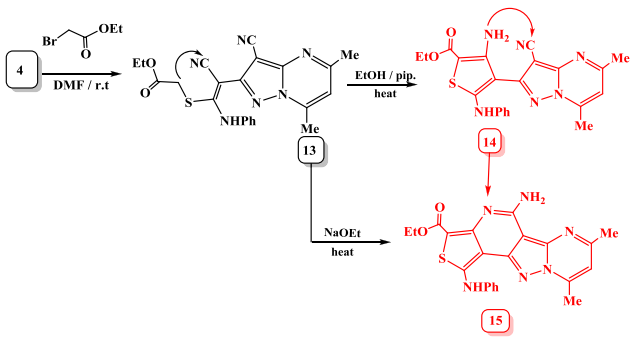
Scheme 3 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



compound **12**. The structure of the isolated product **12** was established by its elemental analyses and spectral data (Experimental section and Scheme 3).

Also, the reaction of compound **4** with ethyl bromoacetate under the same reaction conditions afforded the products **13**, **14**, and **15**, respectively (Scheme 4). The

Scheme 4 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



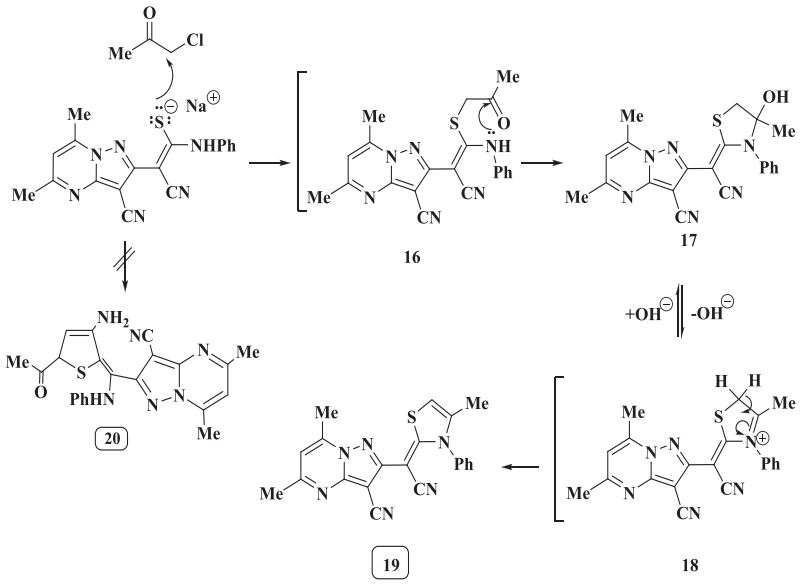
structure of the isolated products was established by elemental analysis and spectral data (Experimental section).

On the other hand, the reaction of the potassium salt **4** with chloroacetone in dimethylformamide at room temperature afforded thiazole derivative **19** rather than the expected thiophene derivative **20** (Scheme 5). The structure of **19** was confirmed on the basis of its elemental analysis and spectral data. The IR spectrum of **19** was found to be free from the amino absorption bands but instead showed nitrile absorption band at ν_{max} 2210 cm^{-1}. The ^1H NMR spectrum revealed a singlet signal at $\delta = 6.92$ ppm due to pyrimidine proton, in addition, a singlet signal at $\delta = 1.86$ ppm assigned to methyl protons, besides the other expected signals. The mass spectrum of **19** showed correct molecular ion peak at m/z 384 [M^+]. Further, an evidence to support the structural assignment of structure **19** was gained from the x-ray crystallographic analysis (Fig. 1).

It is noteworthy to report that the product **19** was alternatively synthesized by the reaction of compound **4** with α-chloroacetylacetone in dimethylformamide at room temperature in the presence of potassium hydroxide solution, to afford a product identical in all respects (IR, mp, and mixed mp) with compound **19** (Scheme 6).

Enamines are interesting class of organic compounds; the special value of these compounds is due to their utility as valuable intermediate for the synthesis of several interesting compounds [19–24]. Based on this finding, we prepared the enamine derivative of compound **3**. Thus, the reaction of **3** with dimethylformamide-dimethylacetal in dry dioxane afforded the corresponding enamine derivative **21** (Scheme 7). The structure of enamine **21** was established by its elemental analysis and spectral data

Scheme 5



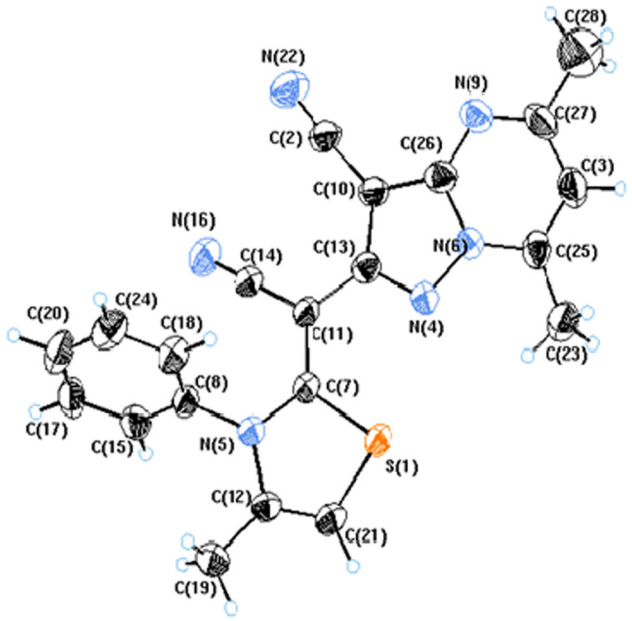
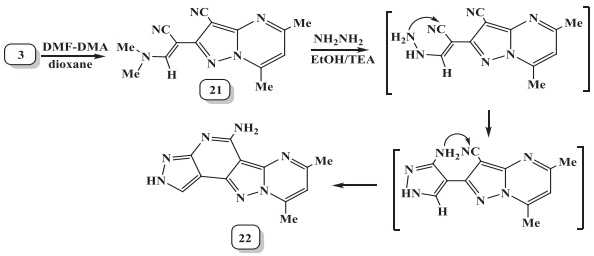


Figure 1 Oak Ridge Thermal Ellipsoid Plot Program (molecular modeling) (ORTEP) drawing of compound **19**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

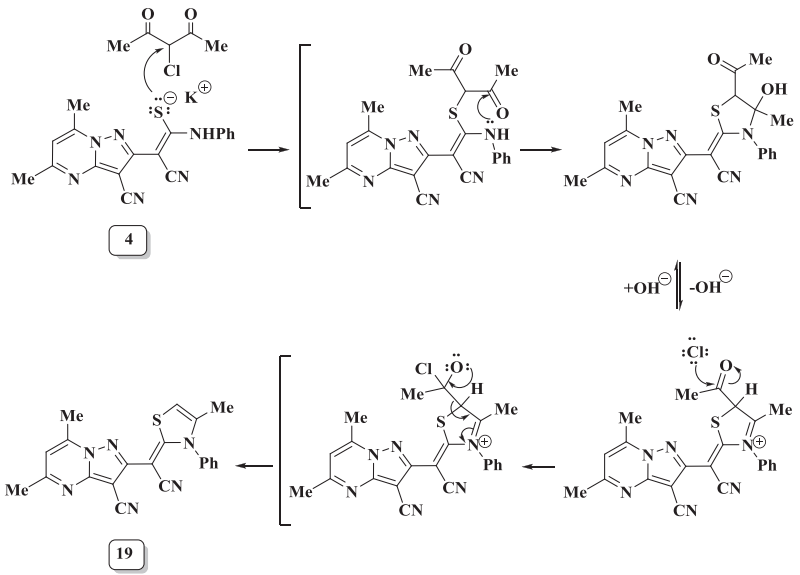
(IR, ^{1}H NMR, and mass spectra (MS)). The IR spectrum of this product showed absorption band at ν_{max} 2206 cm^{-1} for the two cyano groups. The ^{1}H NMR spectrum of **21** revealed the presence of singlet signals assigned to two methyl and CH protons at $\delta = 2.53$, 2.65, and 7.07 ppm, respectively. In addition, two singlet signals at $\delta = 3.13$ and 3.32 ppm were assigned to two methyl protons [$-N(CH_3)_2$] and a singlet signal at $\delta = 7.76$ ppm attributable to olefinic proton. The mass spectrum together with the elemental analysis are in agreement with structure **21**. Treatment of the enamine derivative **21** with hydrazine hydrate in absolute ethanol in the presence of few drops of triethylamine afforded a yellow solid mass. The isolated product **22** was confirmed on the basis of its elemental analysis and spectral data. The IR spectrum of compound **22** revealed no absorption bands corresponding to the two cyano groups and instead appearance of absorption bands at ν_{max} 3376 and 3067 cm^{-1} due to the amino and NH groups. Its ^{1}H NMR spectrum revealed two D_2O-exchangeable signals at $\delta = 9.05$ and 12.96 ppm attributable to NH_2 and NH protons, besides the expected protons. Elemental analysis and mass spectrum are in consistent with structure **22** (Scheme 7).

Similarly, the reaction of enamine derivative **21** with hydroxylamine hydrochloride in absolute ethanol containing anhydrous sodium acetate yielded the novel product **23** (Scheme 8). The structure of the isolated product was confirmed on the basis of its elemental analysis and spectral data (Experimental section).

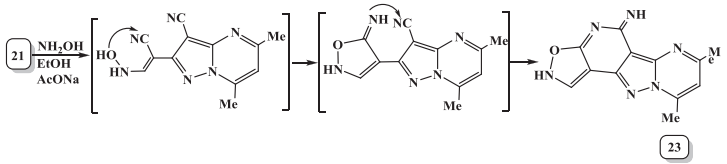
Scheme 7



Scheme 6



Scheme 8



CONCLUSION

A simple route for the synthesis of some novel pyrazolo[1,5-*a*]pyrimidine derivatives and tetraheterocyclic compounds starting from laboratory-available cheap starting material cyano-methyl-1*H*-pyrazole-4-carbonitrile is described.

EXPERIMENTAL

Melting points were determined on an Electrothermal (9100) apparatus and were uncorrected. The IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer (Perkin Elmer, Waltham, MA, USA). ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide at 300 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as internal reference, and the results are expressed as δ value. Mass spectra were taken on a Shimadzu GCMS-GB 1000 Ex mass spectrometer (Shimadzu, Kyoto, Japan) at 70 eV. Elemental analysis was carried out at the Microanalysis Center of Cairo University and was performed on Vario EL III Elemental CHNS analyzer (Germany). X-ray crystallography was carried out at National Research Center, Dokki, Giza, Egypt. The starting compounds **1** and **3** were prepared according to the reported literature [25].

Synthesis of 2-cyanomethyl-5,7-dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbonitrile (3). A mixture of 5-amino-3-cyanomethyl-1*H*-pyrazole-4-carbonitrile (**1**) (0.01 mol) with acetylacetone (**2**) (0.01 mol) in glacial acetic acid (10 mL) was heated under reflux for 12 h and then allowed to cool. The solid was collected by filtration and recrystallized from an ethanol-dioxane mixture to give compound **3** as pale brown crystals, yield 88%, m.p. 234°C [Lit. 227°C], ν_{max}/cm^{-1} (KBr) 2226 (2CN); ^{1}H NMR [dimethyl sulfoxide (DMSO)] $\delta = 2.63$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.53 (2, 2H, CH_2), 7.27 (s, 1H, pyrimidine-H). *Anal*. Calcd for $C_{11}H_9N_5$ (211.23): C, 62.55; H, 4.29; N, 33.16. Found: C, 62.72; H, 4.47; N, 33.38%.

Synthesis of potassium 2-cyano-2-(3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-2-yl)-1-(phenylamino)ethene-1-thiolate (4). To a stirred solution of potassium hydroxide (0.01 mol) in dimethylformamide (10 mL) was added compound **3** (0.01 mol). After 3 h, phenyl isothiocyanate (0.01 mol) was added to the resulting mixture. Stirring was continued overnight at room temperature, and the solid product so formed was collected by filtration, washed with absolute ethanol, and recrystallized from dimethylformamide as yellow crystals, yield 84%, m.p. 365°C, ν_{max}/cm^{-1} (KBr) 3060 (NH), 2215 (CN), and 2171 (CN); ^{1}H NMR (DMSO) $\delta = 2.67$ (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 6.91 (s, 1H, CH), 6.84–7.84 (m, 5H, ArH's), 11.75 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{13}KN_6S$ (384.50): C, 56.23; H, 3.41; K, 10.17; N, 21.86; S, 8.34. Found: C, 56.41; H, 3.60; N, 22.09; S, 8.52%.

Synthesis of 2-[1-cyano-2-(2-aroylmethylthio)-2-(phenylamino) ethenyl]-5,7-dimethyl-[1,5-*a*]pyrimidine-3-carbonitriles (6a–c). ***General procedure.*** To a solution of the thioanilide derivative **4** (0.01 mol) in dimethylformamide (10 mL), the appropriate ω-bromoacetophenone derivatives **6a–c** (0.01 mol) was added. The resulting reaction mixture was left stirred at room temperature overnight. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, and recrystallized from ethanol.

2-[1-Cyano-2-(2-oxo-2-phenylethylthio)-2-(phenylamino)vinyl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (6a). Whitish brown crystals, yield, 80%, m.p. 190°C, ν_{max}/cm^{-1} (KBr) 3181 (NH), 2211 (2CN), and 1674 (CO); ^{1}H NMR (DMSO) $\delta = 2.60$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 6.55 (s, 2H, CH_2), 7.02 (s, 1H, CH), 7.21–7.64 (m, 10H, ArH's), 9.26 (s, 1H, NH). MS: $m/z = 463$ ($M^+ - 1$,100%), 338 (7.7%), 232 (4.7%), 193 (7.4%), 158 (3.4%), 135 (6.1%), 105 (42%), 77 (93%). *Anal*. Calcd for $C_{26}H_{20}N_6OS$: C, 67.22; H, 4.34; N, 18.09; S, 6.90. Found: C, 67.43; H, 4.52; N, 18.32; S, 6.72%.

2-{2-[(2-(4-Chlorophenyl)-2-oxoethyl)thio]-1-cyano-2-(phenyl amino)vinyl}-5,7-dimethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (6b). Whitish brown crystals, yield, 86%, m.p. 205°C, ν_{max}/cm^{-1} (KBr) 3287 (NH), 2214 (2CN), and 1676 (CO); ^{1}H NMR (DMSO) $\delta = 2.70$ (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 7.15 (s, 2H, CH_2), 7.22 (s, 1H, CH), 7.34–8.04 (m, 9H, ArH's.), 9.65 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}ClN_6OS$ (498.99): C, 62.58; H, 3.84; Cl, 7.10; N, 16.84; S, 6.43. Found: C, 62.40; H, 4.02; N, 16.61; S, 6.60%.

2-{2-[2-(4-Bromophenyl)-2-oxoethylthio]-1-cyano-2-(phenylamino)vinyl}-5,7-dimethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (6c). Pale yellow crystals, yield, 83%, m.p. 219 °C, ν_{max}/cm^{-1} (KBr) 3218 (NH), 2222 (2CN), and 1675 (CO); ^{1}H NMR (DMSO) $\delta = 2.68$ (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.12 (s, 2H, CH_2), 7.24 (s, 1H, CH), 7.36–8.11 (m, 9H, ArH's.), 10.12 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}BrN_6OS$: C, 57.46; H, 3.52; Br, 14.70; N, 15.46; S, 5.90%. Found: C, 57.66; H, 3.70; N, 14.94; S, 5.73%.

Conversion of compounds 6a–c into compounds (8a–c). ***General procedure.*** Compounds **6a–c** (0.01 mol) were refluxed in absolute ethanol in presence of few drops of piperidine (as basic catalyst) for 3 h thin layer chromatography (TLC) and then cooled. The solid so formed was filtered off and recrystallized from an ethanol-dioxane mixture.

2-(4-Amino-5-benzoyl-2-(phenylamino)thiophen-3-yl)-5,7-dimethylpyrazolo[1,5-a]-pyrimidine-3-carbonitrile (8a). Whitish brown crystals, yield, 80%, m.p. 290°C, ν_{max}/cm^{-1} (KBr) 3319, 3144 (NH_2 and NH), 2218 (CN), and 1631 (CO); ^{1}H NMR (DMSO) $\delta = 2.56$ (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 7.17 (s, 1H, CH), 7.38–7.56 (m, 12H, ArH's and NH_2), 9.96 (s, 1H, NH). MS: $m/z = 463(M^+ - 1, 100\%)$, 359 (4.8%), 231 (5.3%), 135 (8.2%), 105 (41.2%), 77 (91%). *Anal*. Calcd for $C_{26}H_{20}N_6OS$: C, 67.22; H, 4.34; N, 18.09; S, 6.90. Found: C, 67.44; H, 4.52; N, 18.32; S, 7.08%.

2-[4-Amino-5-(4-chlorobenzoyl)-2-(phenylamino)thiophen-3-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (8b). Whitish brown crystals, yield, 86%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3290, 3028 (NH_2 and NH), 2221 (CN), and 1621 (CO); ^{1}H NMR (DMSO) $\delta = 2.77$ (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.21 (s, H, CH), 7.46–7.60 (m, 11H, ArH's, NH_2), 10.04 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}ClN_6OS$: C, 62.58; H, 3.84; Cl, 7.10; N, 16.84; S, 6.43. Found: C, 62.40; H, 4.02; N, 16.61; S, 6.60%.

2-[4-Amino-5-(4-bromobenzoyl)-2-(phenylamino)thiophen-3-yl]-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (8c). Pale yellow crystals, yield, 83%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3310, 3043 (NH_2 and NH), 2218 (CN), and 1625 (CO); ^{1}H NMR (DMSO) $\delta = 2.68$ (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.16 (s, 1H, CH), 7.38–7.76 (m, 11H, ArH's, NH_2), 10.0 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}BrN_6OS$: C, 57.46; H, 3.52; Br, 14.70; N, 15.46; S, 5.90. Found: C, 57.66; H, 3.70; N, 14.94; S, 5.73%.

Conversion of compounds 6a–c into compounds (9a–c). ***General procedure.*** Compounds **8a–c** (0.01 mol) were refluxed in sodium ethoxide solution for 6 h (TLC) and then cooled. The solid so formed was filtered off and recrystallized from dimethylformamide.

(5-Amino-7,9-dimethyl-1-(phenylamino)thieno[3″,4″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5-a]-pyrimidin-3-yl)(phenyl)methanone (9a). Whitish brown crystals, yield, 60%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3309, 3050 (NH_2 and NH), and 1633 (CO); ^{1}H NMR (DMSO) $\delta = 2.57$ (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.20 (s, 1H, CH), 7.22–7.79 (m, 12H, ArH's, NH_2), 10.06 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{20}N_6OS$ (464.55): C, 67.22; H, 4.34; N, 18.09; S, 6.90. Found: C, 67.44; H, 4.52; N, 18.32; S, 7.08%.

(5-Amino-7,9-dimethyl-1-(phenylamino)thieno[3″,4″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5-a]-pyrimidin-3-yl)(4-chlorophenyl)methanone (9b). Whitish brown crystals, yield, 64%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3290, 3028 (NH_2 and NH), and 1621 (CO); ^{1}H NMR (DMSO) $\delta = 2.77$ (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 7.19 (s, H, CH), 7.46–7.85 (m, 11H, ArH's, NH_2), 10.14 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}ClN_6OS$ (498.99): C, 62.58; H, 3.84; Cl, 7.10; N, 16.84; S, 6.43. Found: C, 62.40; H, 4.02; N, 16.61; S, 6.60%.

(5-Amino-7,9-dimethyl-1-(phenylamino)thieno[3″,4″:5′,6′]pyrido[4′,3′:3,4]pyrazolo[1,5-a]-pyrimidin-3-yl)(4-bromophenyl)methanone (9c). Pale yellow crystals, yield, 63%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3310, 3043 (NH_2 and NH), and 1625 (CO); ^{1}H NMR (DMSO) $\delta = 2.68$ (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.16 (s, 1H, CH), 7.38–7.76 (m, 11H ArH's, NH_2), 10.12 (s, 1H, NH). *Anal*. Calcd for $C_{26}H_{19}BrN_6OS$ (): C, 57.46; H, 3.52; Br, 14.70; N, 15.46; S, 5.90. Found: C, 57.66; H, 3.70; N, 14.94; S, 5.73%.

Synthesis of 2-(2-cyano-2-((cyanomethyl)thio)-1-(phenylamino)vinyl)-5,7-dimethyl-pyrazolo[1,5-a]pyrimidine-3-carbonitrile (10). To a solution of the thioanilide derivative **4** (0.01 mol) in dimethylformamide (10 mL), the chloroacetonitrile (0.01 mol) was added. The resulting reaction mixture was left stirred at room temperature overnight. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, and recrystallized from ethanol as pale brown crystals, yield, 67%, m.p. 138°C, ν_{max}/cm^{-1} (KBr) 3062 (NH), 2210 (CN), and 2218 (2CN); ^{1}H NMR (DMSO) $\delta = 2.67$ (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.18 (s, 2H, CH_2), 7.28 (s, 1H, CH), 7.36–7.63 (m, 5H, ArH's), 10.11 (s, 1H, NH). *Anal*. Calcd for $C_{20}H_{15}N_7S$ (385.45): C, 62.32; H, 3.92; N, 25.44; S, 8.32. Found: C, 62.12; H, 3.74; N, 25.61; S, 8.55%.

Synthesis of 2-(2-amino-5-cyano-4-(phenylamino)thiophen-3-yl)-5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (11). Compound **10** (0.01 mol) was refluxed in ethanol in presence of few drops of piperidine for 3 h (TLC) and then cooled. The solid so formed was filtered off and recrystallized from dimethylformamide as brown crystals, yield, 61%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3368 (NH_2), 3165 (NH), 2213 (CN), and 2211 (CN); ^{1}H NMR (DMSO) $\delta = 2.68$ (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 7.23 (s, 1H, CH), 7.31–7.58 (m, 7H, ArH's, NH_2), 10.02 (s, 1H, NH). *Anal*. Calcd for $C_{20}H_{15}N_7S$: C, 62.32; H, 3.92; N, 25.44; S, 8.32. Found: C, 62.14; H, 4.11; N, 25.20; S, 8.52%.

Synthesis of 5-amino-7,9-dimethyl-1-(phenylamino)thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]-pyrazolo[1,5-a]pyrimidine-2-carbonitrile (12). Compound **11** (0.01 mol) was refluxed in sodium ethoxide solution for 5 h (TLC) and then cooled. The solid so formed was filtered off and recrystallized from dimethylformamide as brown crystals, yield, 61%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3381 (NH_2), 3210 (NH), 2212 (CN), and 1621 (C=N); ^{1}H NMR (DMSO) $\delta = 2.67$ (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 7.31 (s, 1H, CH), 7.43–7.67 (m, 7H, ArH's, NH_2), 10.11 (s, 1H, NH). *Anal*. Calcd for $C_{20}H_{15}N_7S$: C, 62.32; H, 3.92; N, 25.44; S, 8.32. Found: C, 62.14; H, 4.11; N, 25.20; S, 8.52%.

Synthesis of ethyl-2-[2-cyano-2-(3-cyano-5,7-dimethyl-8-hydropyrazolo[1,5-a]pyrimidin-2-yl)-1-(phenylamino)vinylthio]acetate (13). To a solution of the thioanilide derivative **4** (0.01 mol) in dimethylformamide (10 mL), the ethyl bromoacetate (0.01 mol) was added. The resulting reaction mixture was left stirred at room temperature overnight. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, and recrystallized from

ethanol as pale yellow crystals, yield, 85%, m.p. 166°C, ν_{max}/cm^{-1} (KBr) 3185 (NH), 2219 (CN), 2197 (CN), and 1733 (CO); ^{1}H NMR (DMSO) $\delta = 1.16$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.69 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 4.12 (q, 2H, $J = 7.2$ Hz, CH_2), 6.82 (s, 2H, CH_2), 7.10 (s, 1H, CH), 7.0–7.55 (m, 5H, ArH's), 10.12 (s, 1H, NH). MS: $m/z = 432$ (M^+, 75.5%), 386 (100%), 313 (57.8%), 211 (44.2%), 183 (13.1%), 160 (10%), 119 (7.4%). *Anal*. Calcd for $C_{22}H_{20}N_6O_2S$: C, 61.10; H, 4.66; N, 19.43; S, 7.41. Found: C, 61.28; H, 4.86; N, 19.70; S, 7.58%.

Synthesis of ethyl 5-amino-1-imino-8,10-dimethyl-2-phenyl-2,7-dihydro-pyrimidino[1′,2′-5,1]pyrazolo-[3,4-d]thiopheno[2,3-b]pyridine-4-carboxylate (14). Compound **13** (0.01 mol) was refluxed in ethanol in presence of few drops of piperidine for 3 h (TLC) and then cooled. The solid so formed was filtered off and recrystallized from dimethylformamide as pale rose crystals, yield, 80%, m.p. 320°C, ν_{max}/cm^{-1} (KBr) 3373, 3060 (NH and NH_2), and 1670 (CO); ^{1}H NMR (DMSO) $\delta = 1.20$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.74 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 4.13 (q, 2H, $J = 7.2$ Hz, CH_2), 6.59 (s, 2H, NH_2), 7.17 (s, 1H, CH), 7.46–7.61 (m, 5H, ArH's), 10.32 (s, 1H, NH). MS: $m/z = 431$ ($M^+ - 1$, 100%), 385 (14.6%), 359 (24.8%), 312 (4%), 281 (8.8%), 237 (8.7%), 211 (3.5%), 193 (8.4%), 172 (4.3%), 131 (2.1%), 113 (2.3%), 77 (2.75%). *Anal*. Calcd for $C_{22}H_{20}N_6O_2S$: C, 61.10; H, 4.66; N, 19.43; S, 7.41. Found: C, 61.26; H, 4.84; N, 19.21; S, 7.63%.

Synthesis of 5-amino-7,9-dimethyl-1-(phenylamino)thieno[3″,2″:5′,6′]pyrido[4′,3′:3,4]-pyrazolo[1,5-a]-pyrimidine-2-carbonitrile (15). Compound **15** (0.01 mol) was refluxed in sodium ethoxide solution for 5 h (TLC) and then cooled. The solid so formed was filtered off and recrystallized from dimethylformamide as brown crystals, yield, 58%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3332 (NH_2), 3196 (NH), and 1621 (C=N); ^{1}H NMR (DMSO) 1.20 (t, 3H, $J = 6.9$ Hz, CH_3), 2.70 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.13 (q, 2H, $J = 6.9$ Hz, CH_2), 7.21 (s, 1H, CH), 7.38–7.63 (m, 7H, ArH's, NH_2), 10.21 (s, 1H, NH). *Anal*. Calcd for $C_{22}H_{20}N_6O_2S$: C, 61.10; H, 4.66; N, 19.43; S, 7.41. Found: C, 61.29; H, 4.88; N, 19.68; S, 7.23%.

2-(Cyano(4-methyl-3-phenylthiazol-2(3H)-ylidene)methyl)-5,7-dimethylpyrazolo[1,5-a]-pyrimidine-3-carbonitrile (19). To a solution of the thioanilide derivative **4** (0.01 mol) in dimethylformamide (10 mL), the chloroacetone (0.01 mol) was added. The resulting reaction mixture was left stirred at room temperature overnight. The reaction mixture was poured onto ice water. The solid so formed was filtered off, washed with water, and recrystallized from an ethanol-dioxane mixture.

Alternate synthesis of compound 19. To a solution of the thioanilide derivative **4** (0.01 mol) in dimethylformamide (10 mL) containing potassium hydroxide solution (0.01 mol), the α-chloroacetylacetone (0.01 mol) was added. The resulting reaction mixture was left stirred at room temperature overnight. The reaction mixture was poured with water. The solid so formed was filtered off, washed with water, and recrystallized from an ethanol-dioxane mixture as yellow crystals, yield, 76%, m.p. 305°C, ν_{max}/cm^{-1} (KBr) 2210 and 2185 (CN); ^{1}H NMR (DMSO) $\delta = 1.86$ (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 6.92 (s, 1H, CH), 7.09 (s, 1H, CH), 7.50–7.60 (m, 5H, ArH's). MS: $m/z = 384$ (M^+, 100%). *Anal.* Calcd for $C_{21}H_{16}N_6S$: C, 65.61; H, 4.19; N, 21.86; S, 8.34. Found: C, 65.82; H, 4.37; N, 21.62; S, 8.52%.

Synthesis of 2-[2-(dimethylamino)-1-cyano-vinyl]-5,7-dimethyl pyrazolo[1,5-a]pyrimidine-3-carbonitrile (21). mixture of compound **3** (0.01 mol) and dimethylformamide-dimethylacetal (0.01 mol) in 20 mL dry dioxane was refluxed for 5 h and then left to cool. The resulting solid was collected by filtration, washed with methanol, and recrystallized from an ethanol-dioxane mixture to afford the respective enamine derivative **21** as orange crystals, yield, 75%, m.p. 245°C, ν_{max}/cm^{-1} (KBr) 2206 (2CN); ^{1}H NMR (DMSO) $\delta = 2.53$ (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 7.06 (s, 1H, CH), 7.76 (s, 1H, CH). MS: $m/z = 266$ (M^+, 100%), 251 (46.5%), 236 (18.9%), 224 (19.9%), 197 (10.9%), 172 (13.8%), 133 (14%), 120 (11.2%), 108 (23.2%), 80 (22.4%), 67 (20.8%). *Anal.* Calcd for $C_{14}H_{14}N_6$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.32; H, 5.49; N, 31.33%.

Synthesis of 8,10-dimethyl-7-hydropyrazolo[3,4-b]pyrimidino [1′,2′-5,1]pyrazolo-[3,4-d]-pyridinylamine (22). A mixture of compound **21** (0.01 mol) and hydrazine hydrate (0.015 mol) in absolute ethanol containing few drops of triethylamine was refluxed for 2 h, and the reaction mixture was cooled. The solid that precipitated was filtered off and recrystallized from dimethylformamide.

Yellow crystals, yield, 72%, m.p. 295°C, ν_{max}/cm^{-1} (KBr) 3376 and 3067 (NH and NH_2); ^{1}H NMR (DMSO) $\delta = 2.77$ (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 6.95 (s, 1H, CH), 7.41 (s, 1H, CH), 9.05 (s, 2H, NH_2), 12.96 (br., 1H, NH). MS: $m/z = 253$ (M^+, 100%). *Anal.* Calcd for $C_{12}H_{11}N_7$: C, 56.91; H, 4.38; N, 38.71. Found: C, 56.72; H, 4.56; N, 38.93%.

Synthesis of 8,10-dimethyl-4,7-dihydroisoxazolo[5″,4″-2′,3′] pyridino[4′,5′-3,4]pyrazolo-[1,5-a]pyramidinimine (23). To a solution of compound **21** (0.01 mol) in absolute ethanol were added hydroxylamine hydrochloride (0.01 mol) and sodium acetate anhydrous (0.01 mol). The reaction was refluxed for 3 h. The solid product was filtered off and recrystallized from dimethylformamide.

Pale orange crystals, yield, 69%, m.p. 300°C, ν_{max}/cm^{-1} (KBr) 3385 (NH); ^{1}H NMR (DMSO) $\delta = 2.73$ (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 7.22 (s, 1H, CH), 7.79 (s, 1H, CH), 8.64 (s, 1H, NH), 10.78 (s, 1H, NH). MS: $m/z = 254$ (M^+, 100%). *Anal.* Calcd for $C_{12}H_{10}N_6O$: C, 56.69; H, 3.96; N, 33.05. Found: C, 56.88; H, 3.78; N, 33.27%.

X-ray structure determination of compound 19. The x-ray diffraction measurement was made on using maXus (Bruker Nonius, Delft and MaScience, Japan) at temperature 298 K and wavelength 0.71073 Å; radiation: Mo *Ka*. Crystal data for compound **19**; $C_{21}H_{16}N_6S$, $M_r = 384.465$, crystal system, space group: monoclinic, C2/c;

unit cell dimensions: $a = 21.5557$ (**3**) Å, $b = 14.6811$ (**3**) Å, $c = 15.8913$ (**3**) Å, $\alpha = 90.00^{\circ}$, $\beta = 131.0434$ (**8**)$^{\circ}$, $\gamma = 90.00^{\circ}$; volume: 3792.92 (**12**) Å^3; $Z = 8$; calculated density: 1.347 Mg/m^{-3}; absorption coefficient: $\mu = 0.19\,mm^{-1}$; reflection 3139 measured, $\theta max = 29.13^{\circ}$; ωR factor = 0.11.

Crystallographic data for the structural analysis of compound **19** have been deposited with the Cambridge Crystallographic Data Centre under the number 794626. Copies of the information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-01223-336033; e-mail: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam.ac.uk).

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