

Article

Synthesis of 5-Substituted 3-Amino-1*H*-Pyrazole-4-Carbonitriles as Precursors for Microwave Assisted Regiospecific Syntheses of Pyrazolo[1,5-*a*]Pyrimidines

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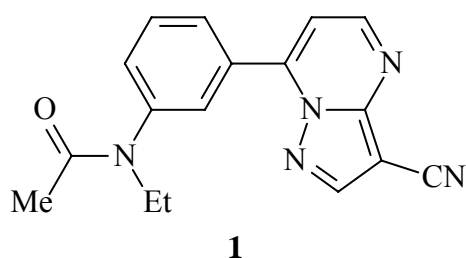
Abstract: A simple route to 3-oxoalkanonitrile **5**, a precursor of the title compounds is described. Reaction of enaminones **2** with hydroxylamine hydrochloride in ethanol yielded aldoximes **3** that were converted readily into **5** in basic medium. This method has been successfully applied with a number of substrates and resulted in excellent yields of the products. Reacting **5** with trichloroacetonitrile afforded 3-amino-2-aroyl-4,4,4-trichloro-2-butenenitriles **6** that condensed with hydrazines to yield 3-amino-1*H*-pyrazole-4-carbonitrile derivatives **8**. Substituted pyrazolo[1,5-*a*]pyrimidines have been prepared with regioselective condensation reactions of **8** with nonsymmetrical dielectrophiles. The structures of compounds obtained were deduced based on ¹H-NMR, ¹H-¹⁵N HMBC- measurements.

Keywords: Oxoalkanonitriles; 2-Aroyl-3-dimethylamino-2-propenenitrile; Pyrazolo[1,5-*a*]pyrimidines; Solvent-free reactions; ¹H-¹⁵N HMBC.

Introduction

Interest in pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile derivatives has been reviewed [1-3]. Among them are zaleplon (**1**, Figure 1) analogues, that have been classified as sedative/hypnotic drugs, and as such, are expected to possess considerable biological activity [4-6]. With the aim of obtaining compounds possessing the above properties, we examined the condensation of 5-substituted 3-amino-1*H*-4-pyrazolecarbonitriles **8** with bidentate electrophiles and investigated if such compounds would facilitate regioselective syntheses of substituted 7-aryl-pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles that are structurally related to compound **1**. Compound **8a** is readily available from the reaction of 3-oxo-3-phenylpropanenitrile **5a** with trichloroacetonitrile followed by condensation with hydrazine hydrate [7]. This methodology was extended and adapted to the synthesis of several 5-substituted aryl and heteroaryl-pyrazolecarbonitriles using oxoalkanonitriles as precursors. We initially investigated developing a novel route to 3-oxoalkanonitrile derivatives **5**.

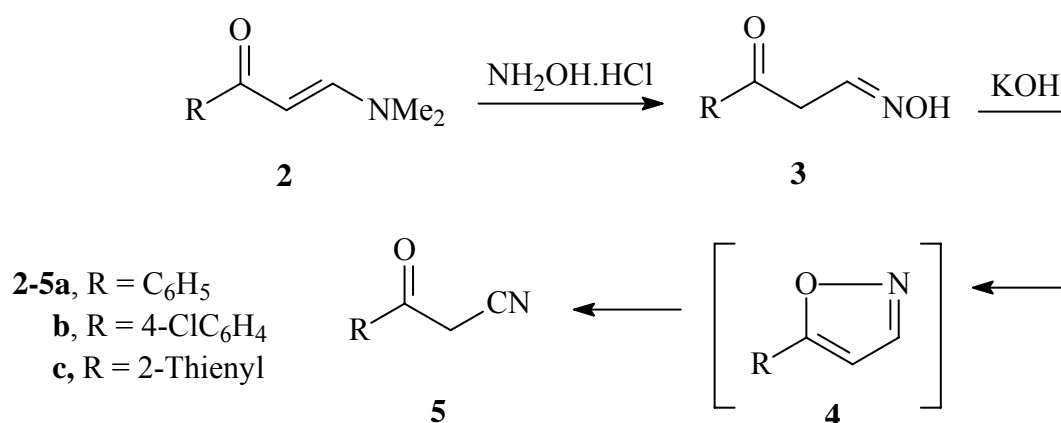
Figure 1. Zaleplon.



Results and Discussion

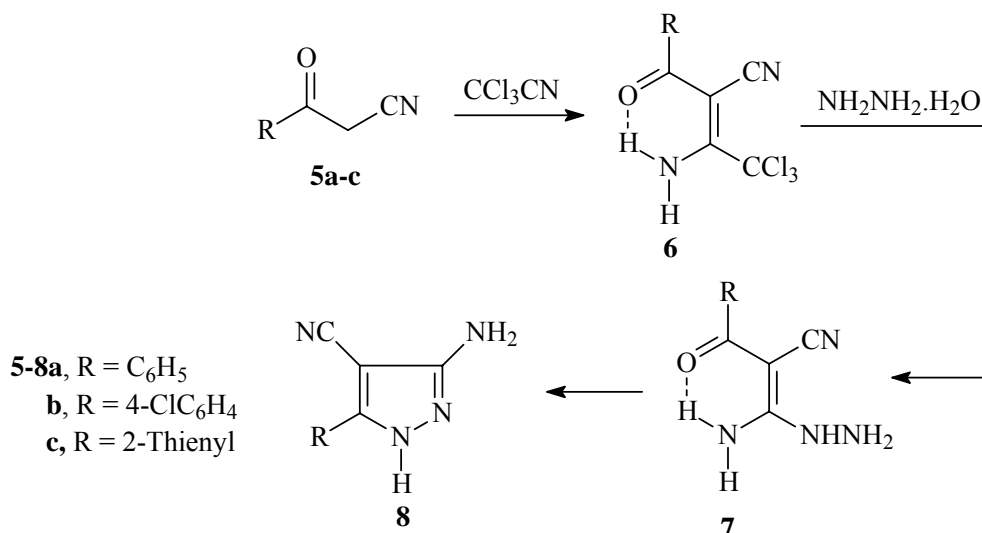
Recently we reported that the reaction of enaminones **2** with hydroxylamine hydrochloride gave the aldoximes **3** in good yields. These were converted to oxoalkanonitriles **5** *via* treatment with diethyl oxalate in the presence of sodium hydride [8]. We now describe a second more efficient process for the preparation of **5** by addition of a solution of hydroxylamine hydrochloride to enaminones **2a-c** in alcoholic KOH. Such a transformation apparently results *via* initial formation of an isoxazole **4** that then undergoes base catalyzed ring opening furnishing **5a-c** (cf. Scheme 1).

Scheme 1. Synthesis of 3-oxo-3-arylpropanenitriles **5a-c** from enaminones **2a-c**.



The oxoalkanonitrile derivatives **5a-c** so obtained were reacted with trichloroacetonitrile to yield adducts **6a-c**. Condensation of these adducts with hydrazine hydrate afforded **7a-c**, that cyclized under reflux in dioxane yielding **8a-c** in good yields (cf. Scheme 2). The doublet splitting of amino group signals observed in the $^1\text{H-NMR}$ spectra of adducts **6a-c** at ca. $\delta_{\text{H}} = 10$ and 12 ppm indicates a non-equivalence of the amino protons, which is probably related to the involvement of one amino proton in an intramolecular H-bond with the carbonyl moiety. Similar features were observed in **7a-c** at ca. $\delta_{\text{H}} = 9$ and 10 ppm. There are alternative procedures described in the literature for the preparation of **8a,b** by treating arylmethylenemalononitrile with hydrazine [9,10] or *via* transformation of isothiazoles and isoxazoles into pyrazoles **8a,b** using hydrazines [11]. In the present article, the condensation reaction of 3-amino-1*H*-4-pyrazolecarbonitrile derivatives **8a-c** with enaminone **2c** and enamionitrile **9**, recently prepared in our laboratory [12], is examined.

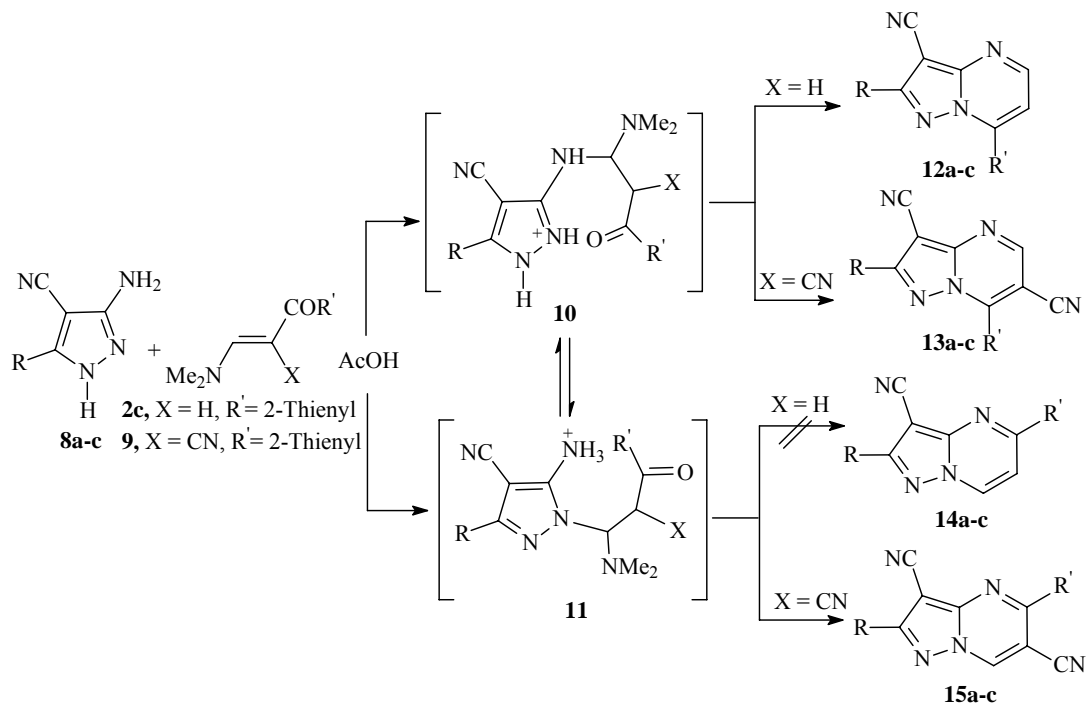
Scheme 2. Synthesis of 3-amino-5-aryl-1*H*-4-pyrazolecarbonitrile **8a-c** from 3-oxo-3-arylpropanenitrile **5a-c**.



The site at which nucleophiles attack occurs on 1*H*-3-aminopyrazole derivatives has been a subject of considerable debate in the past [13-14]. Reactions of unsymmetrical 1,3-diketones with 3(5)-aminopyrazoles often lead to the formation of inseparable mixtures of two regioisomeric pyrazolo[1,5-*a*]pyrimidines due to comparable reactivity's of the two electrophilic centers in the initial diketone. Recently, use of 1,3-dimethyluracil as the electrophile was reported to involve the attack on both endocyclic and exocyclic nitrogen affording either the pyrazolo[1,5-*a*]pyrimidin-5-one or 7-one isomers, depending on the reaction conditions [15], whereas the reaction of 1*H*-3-aminopyrazole with benzylidenemalononitrile [16] and with 1-arylbutane-1,3-diones [17] are established to involve exocyclic amino group. It is thought that there is an equilibrium between possible initial attack at the ring nitrogen and the exocyclic amino group. Structures of the products resulting from reactions of α,β -unsaturated compounds with aminoazoles should be determined in each case, as the outcome of the reactions would be dependent on several factors, including steric consideration, relative basicities and solubility of both isomers in reaction medium. Although it is generally accepted that 3(5)-aminopyrazoles reacts with enaminones to yield the 7-substituted isomers, we noticed that this pattern is not always followed, as the reaction product proved to be dependent on both reaction conditions as

well as nature of reagents. In the present article we have found that reaction of **8a-c** with enaminonitrile **2c** in acetic acid at reflux temperature over a long period of time resulted in selective formation of pyrazolo[1,5-*a*]pyrimidines derivatives in good yields (cf. Scheme 3).

Scheme 3. Proposed mechanism for the formation of pyrazolo[1,5-*a*]pyrimidines **12a-c**, **13a-c** and **15a-c** in acetic acid.

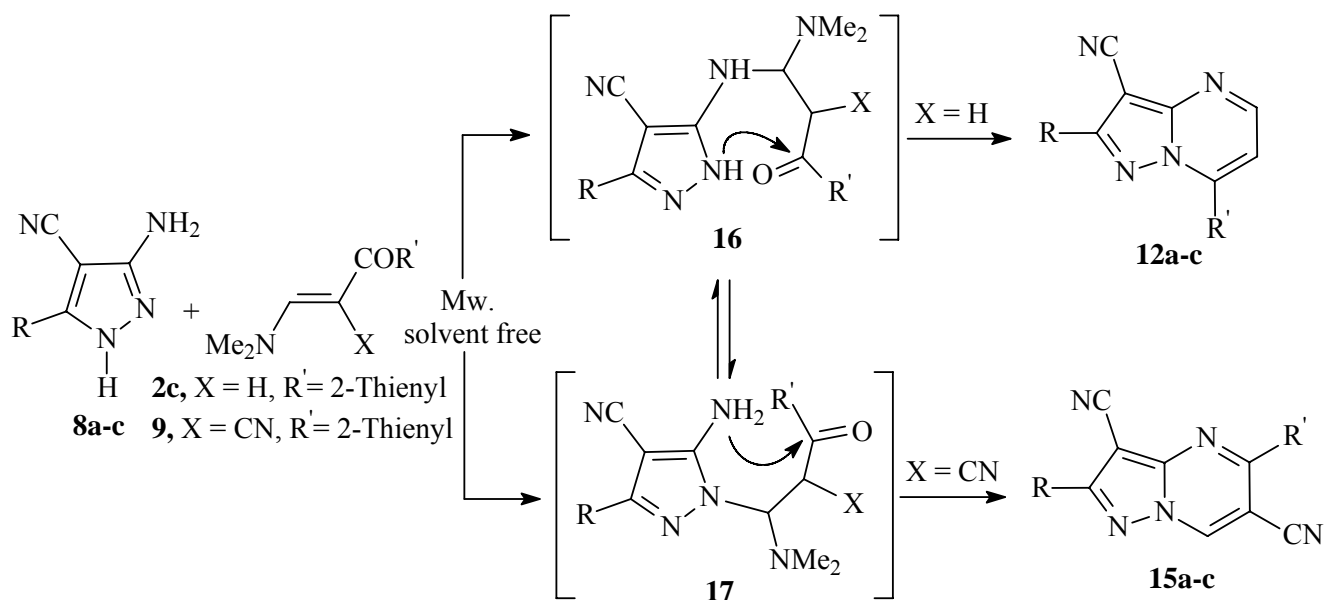


The $^1\text{H-NMR}$ spectra gave no reliable information on the structure of the products; on the other hand they indicate that only one of the possible isomeric structures, **12** or **14**, are formed, rather than their mixture. The condensation products were assigned structures **12a-c** on the basis of $^1\text{H-}^{15}\text{N}$ HMBC measurements. For example compound **12a**, showed chemical shifts for N-7a at $\delta (^{15}\text{N}) = 215$ ppm, N-4 at $\delta (^{15}\text{N}) = 268$ ppm. and N-1 at $\delta (^{15}\text{N}) = 285$ ppm. Cross peak correlations for the coupling of the shielded proton H-6 at $\delta (^1\text{H}) = 8.05$ ppm is observed with N-7a at $\delta (^{15}\text{N}) = 215$ ppm 3J (H-6, N-7a), N-4 at $\delta (^{15}\text{N}) = 268$ ppm 3J (H-6, N-4) and with N-1 at $\delta (^{15}\text{N}) = 285$ ppm 4J (H-6, N-1). Coupling of the deshielded proton at $\delta (^1\text{H}) = 8.83$ ppm with N-7a at $\delta (^{15}\text{N}) = 215$ ppm 4J (H-5, N-7a) and with N-4 at $\delta (^{15}\text{N}) = 268$ ppm 2J (H-5, N-4) are also observed. Alternative structure **14** would show coupling of the deshielded H-7 proton to be with N-1 in the spectrum at $\delta (^{15}\text{N}) = 285$ ppm. The correlations in the $^1\text{H-}^{15}\text{N}$ HMBC measurements for compounds **12b,c** showed similar coupling correlations as **12a**. Reaction of 3-amino-5-aryl-1H-4-pyrazolecarbonitriles **8a-c** with enaminonitrile **9** (X = CN) in acetic acid under the same reaction conditions afforded a mixture of (5)7-substituted pyrazolo[1,5-*a*]pyrimidine derivatives **13a-c** and **15a-c**, which could not be separated by chromatographical means. Both isomers showed the same molecular weights in LC-MS. Moreover, the $^1\text{H-NMR}$ spectra of the reaction products of **8a-c** with **9** showed two singlets for two deshielded protons at ca. $\delta_{\text{H}} = 9.0$ and 9.3 ppm. Based on these data, it is concluded that the compounds obtained are isomeric mixtures of **13** and **15**, whose ratio (approximately 1:3) was estimated by integration of the deshielded protons in the corresponding $^1\text{H-NMR}$ spectra. Apparently, in AcOH where the aminopyrazoles are most likely

protonated, both adducts **10** and **11** are formed, as outlined in Scheme 3. Competing cyclization leading to the 5-isomer would also be possible and mixtures are thus formed.

On the other hand, reaction of 3-amino-5-aryl-1*H*-4-pyrazolecarbonitriles **8a-c** with enaminonitrile **9** ($X = \text{CN}$) by heating in a direct beam microwave oven and under solvent free conditions proceeded regioselectively to yield the 5-substituted pyrazolo[1,5-*a*]pyrimidine-3-carbonitrile derivatives **15a-c** in good yield. The addition reaction occurs in a manner different to the formation of the 7-substituted pyrazolo[1,5-*a*]pyrimidine derivatives, as outlined in Scheme 4. The structure **15** of the products obtained was assigned on the basis of ^1H - ^{15}N HMBC measurements. The major discrepancy between the two isomers **13** and **15** was the cross peak correlation observed between the deshielded proton at δ (^1H) = 9.06 ppm with N-1 at δ (^{15}N) = 283 ppm, 3J (H-7, N-1). Alternate structure **13** in which the deshielded proton is on C-5, would not show this correlation and thus structure **13** could be ruled out. There is no doubt that adducts at both exocyclic and endocyclic nitrogen atoms occur, but in this case, the latter cyclize more readily into the 5-substituted pyrazolo[1,5-*a*]pyrimidines derivatives thus shifting the equilibrium. It should be noted that the isomers **12a-c** were also obtained as sole products when the reactions of **8a-c** with **2c** was carried out by heating in a direct beam microwave oven and under solvent free conditions.

Scheme 4. Cyclocondensation reaction of **8a-c** with **2c** and **9** by heating in a direct beam microwave oven and solvent free conditions resulted in selective formation of pyrazolo[1,5-*a*]pyrimidines **12a-c** and **15a-c**.



The behavior of **8a-c** with **9** under microwave irradiation may be attributed to the formation of hot spots that affect the reaction selectivity due to the increase in heating rate. This may lead to the formation of thermodynamically stable products in preference to the kinetic ones [18, 19]. One can thus conclude that this solvent-free reactions proceeds in a regioselective fashion by the relative reactivity of exocyclic nitrogen and ring nitrogen atoms.

Experimental

General

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Microwave mediated chemistry was conducted in heavy-walled Pyrex tubes fitted with PCS cap. and performed with a single mode cavity Explorer Microwave Synthesizer (CEM Corporation, NC, USA), producing continuous irradiation and equipped with simultaneous external air-cooling system. Elemental analyses were obtained on a LECO CHNS-932 Elemental Analyzer. $^1\text{H-NMR}$ spectra were obtained in $\text{DMSO-}d_6$ on a Bruker DPX 400 MHz superconducting spectrometer in $\text{DMSO-}d_6$ with TMS as an internal standard. Two-dimensional NMR spectra were determined on Bruker Avance II 600 MHz superconducting spectrometer in $\text{DMSO-}d_6$ and FT-IR measurements were recorded in KBr disks on a Perkin Elmer 2000 FT-IR system. Mass spectrometric analyses were recorded on a VG-Autospec-Q high performance tri-sector GC/MS/MS.

General procedure for the preparation of compounds **5a-c**

A mixture of each enaminone **2a-c** (10 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.69 g, 10 mmol) in EtOH (30 mL), was added a solution of KOH (5.60 g, 10 mmol) in H_2O (8 mL). The reaction mixture was heated under reflux and deemed completed when the yellow color of the solution changed to brown (in 30-60 min.). The reaction mixtures were then poured onto water and neutralized with HCl. The solid products so obtained were collected by filtration and crystallized from benzene.

3-Oxo-3-phenylpropanenitrile (5a): White crystals, yield (89 %, 1.30 g); mp 79-81 °C (Lit. [12-13] mp. 80-82); IR (cm^{-1}): 2255 (CN) and 1689 (CO); MS m/z (M^+) = 145; $^1\text{H-NMR}$: δ = 4.78 (s, 2H, CH_2), 7.57 (t, 2H, J = 6.8 Hz, Ph-H), 7.72 (t, 1H, J = 7.4 Hz, Ph-H), 7.94 (d, 2H, J = 6.8 Hz, Ph-H); Anal. calcd. for $\text{C}_9\text{H}_7\text{NO}$: (145.16): C, 74.47; H, 4.86; N, 9.65. Found: C, 74.50; H, 4.75; N, 9.57.

3-(4-Chlorophenyl)-3-oxopropanenitrile (5b): Yellow crystals, yield (86 %, 1.54 g); mp 126-128 °C (Lit. [12-13] mp. 128 °C); IR (cm^{-1}): 2255 (CN) and 1680 (CO); MS m/z (M^+) = 179; $^1\text{H-NMR}$: δ = 4.75 (s, 2H, CH_2), 7.60 (d, 2H, J = 8.1 Hz, arom-H), 7.75 (d, 2H, J = 8.3 Hz, arom-H); Anal. calcd. for $\text{C}_9\text{H}_6\text{ClNO}$: (179.01): C, 60.19; H, 3.37; N, 7.80. Found: C, 59.87; H, 3.30; N, 7.67.

3-Oxo-3-(2-thienyl)propanenitrile 5c: Yellow crystals, yield (88 %, 1.32 g); mp 112-114 °C (Lit. [12-13] mp. 110-112 °C); IR (cm^{-1}): 3243 (NH_2), 2255 (CN) and 1666 (CO); MS m/z (M^+) = 151; $^1\text{H-NMR}$: δ = 4.72 (s, 2H, CH_2), 7.30 (t, 1H, J = 4.4 Hz, thienyl H-4), 7.99 (d, 1H, J = 4.8 Hz, thienyl H-3), 8.14 (d, 1H, J = 4.8 Hz, thienyl H-5); Anal. calcd. for $\text{C}_7\text{H}_5\text{NOS}$: (151.19): C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.72; H, 3.31; N, 9.28; S, 21.00.

General procedure for the preparation of compounds 6a-c

To a stirred mixture of each of oxoalkanonitrile **5a-c** (10 mmol) in EtOH (20 mL) and in the presence of anhydrous NaOAc (1 g), was added 3,3,3-trichloropropanenitrile (10 mmol, 1.57 g). The resulting mixture was stirred for six hrs at r.t., then evaporated under vacuum to half its volume. The reaction mixture was then poured onto water. The solid product obtained was collected by filtration and crystallized from ethanol.

(Z)-3-Amino-2-benzoyl-4,4,4-trichloro-2-butenenitrile (**6a**): Pale yellow crystals, yield (82 %, 2.36 g); mp 182-184 °C; IR (cm⁻¹): 3267 and 3250 (NH₂), 2210 (CN) and 1613 (CO); MS m/z (M⁺¹) = 288; ¹H-NMR: δ = 7.48 (t, 2H, *J* = 7.8 Hz, Ph-H), 7.57 (t, 1H, *J* = 7.9 Hz, Ph-H), 7.68 (d, 2H, *J* = 7.8 Hz, Ph-H), 9.96 (s, 1H, NH₂), 11.94 (s, 1H, NH₂); Anal. calcd. for C₁₁H₇Cl₃N₂O: (289.55): C, 45.63; H, 2.44; N, 9.67. Found: C, 45.90; H, 2.41; N, 9.56.

(Z)-3-Amino-4,4,4-trichloro-2-(4-chlorobenzoyl)-2-butenenitrile (**6b**): Yellow crystals, yield (76 %, 2.46 g); mp 221-222 °C; IR (cm⁻¹): 3260 (NH₂), 2214 (CN) and 1610 (CO); MS m/z (M⁺¹) = 322; ¹H-NMR: δ = 7.58 (d, 2H, *J* = 8.0 Hz, arom-H), 7.71 (d, 2H, *J* = 8.2 Hz, arom-H), 10.05 (s, 1H, NH₂), 11.87 (s, 1H, NH₂); Anal. calcd. for C₁₁H₆Cl₄N₂O: (323.99): C, 40.78; H, 1.87; N, 8.65. Found: C, 40.90; H, 2.02; N, 8.80.

(Z)-3-Amino-4,4,4-trichloro-2-(thiophene-2-carbonyl)-2-butenenitrile (**6c**): Brown crystals, yield (85 %, 2.50 g); mp 168-170 °C; IR (cm⁻¹): 3243 (NH₂), 2216 (CN) and 1624 (CO); MS m/z (M⁺¹) = 294; ¹H-NMR: δ = 7.25 (t, 1H, *J* = 4.0 Hz, thienyl H-4), 8.01 (d, 1H, *J* = 5.2 Hz, thienyl H-3), 8.17 (d, 1H, *J* = 4.0 Hz, thienyl H-5), 9.96 (s, 1H, NH₂), 12.01 (s, 1H, NH₂); Anal. calcd. for C₉H₅Cl₃N₂OS: (295.57): C, 36.57; H, 1.71; N, 9.48; S, 10.85. Found: C, 36.25; H, 1.96; N, 9.25; S, 10.50.

Reaction of 6a-c with hydrazine hydrate for the preparation of 7a-c

To each compound **6a-c** (10 mmol), excess hydrazine hydrate (3 mL) was added and stirred for 3 min. (exothermic reaction). The reaction mixture is then allowed to cool to ambient temperature. During time a precipitate is formed that was filtered off and recrystallized from ethanol.

(E)-3-Amino-2-benzoyl-3-hydrazino-2-propenenitrile (**7a**): This compound was obtained as white crystals, yield (93 %, 1.90 g); mp 143-145 °C; IR (cm⁻¹): 3444, 3345 and 3209 (NH and NH₂), 2182 (CN) and 1656 (CO); MS m/z (M)⁺ = 202; ¹H-NMR: δ = 4.72 (s, 2H, NH₂), 7.38-7.46 (m, 3H, arom. H), 7.48 (br s, 1H, NH), 7.58 (d, 2H, *J* = 7.8 Hz, arom-H), 8.51 (s, 1H, NH₂), 9.69 (s, 1H, NH₂); Anal. calcd. for C₁₀H₁₀N₄O: (202.21): C, 59.40; H, 4.98; N, 27.71. Found: C, 59.36; H, 5.2; N, 27.95.

(E)-3-Amino-2-(4-chlorobenzoyl)-3-hydrazino-2-propenenitrile (**7b**): Beige crystals, yield (89 %, 2.10 g); mp 238-240 °C; IR (cm⁻¹): 3387, 3350 and 3305 (NH and NH₂), 2185 (CN) and 1646 (CO); MS m/z (M)⁺ = 236; ¹H-NMR: δ = 4.73 (s, 2H, NH₂), 7.48 (d, 2H, *J* = 8.0 Hz, arom-H), 7.53 (br s, 1H,

NH), 7.59 (d, 2H, $J = 8.0$ Hz, arom-H), 8.54 (s, 1H, NH₂), 9.97 (s, 1H, NH₂); Anal. calcd. for C₁₀H₉ClN₄O: (236.66): C, 50.75; H, 3.83; N, 23.67. Found: C, 50.81; H, 3.92; N, 23.38.

(*Z*)-3-Amino-3-hydrazino-2-(2-thienylcarbonyl)-2-propenenitrile (**7c**): Beige crystals, yield (94 %, 1.95 g); mp 175-177 °C; IR (cm⁻¹): 3449, 3331 and 3217 (NH and NH₂), 2189 (CN) and 1659 (CO); MS m/z (M)⁺ = 208; ¹H-NMR: $\delta = 4.72$ (s, 2H, NH₂), 7.14 (t, 1H, $J = 4.0$ Hz, thienyl H-4), 7.55 (br s, 1H, NH), 7.76 (d, 1H, $J = 4.8$ Hz, thienyl H-3), 7.90 (d, 1H, $J = 4.2$ Hz, thienyl H-2), 8.54 (s, 1H, NH₂), 9.98 (s, 1H, NH₂); Anal. calcd. for C₈H₈N₄OS: (208.24): C, 46.14; H, 3.87; N, 26.90; S, 15.40. Found: C, 45.89; H, 4.09; N, 26.59; S, 15.25.

General procedure for the preparation of compounds **8a-c**

Each compound **7a-c** (10 mmol) was refluxed in dioxane (20 mL) for 30 min. then left to cool at r.t. The target compounds separated as crystals that were collected by filtration and crystallized from the appropriate solvent.

3-Amino-5-phenyl-1H-4-pyrazolecarbonitrile (**8a**): Buff crystals from dioxane, yield (93 %, 1.71 g) mp 200-202 °C; IR (cm⁻¹): 3348, 3303 (NH₂), 3193 (NH) and 2230 (CN); MS m/z (M)⁺ = 184; ¹H-NMR: $\delta = 6.50$ (s, 2H, NH₂), 7.41-7.46 (m, 3H, arom. H), 7.80 (d, 2H, $J = 7.2$ Hz, arom-H), 12.16 (br s, 1H, NH); Anal. calcd. for C₁₀H₈N₄: (184.20): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.03; H, 4.57; N, 30.12.

3-Amino-5-(4-chlorophenyl)-1H-4-pyrazolecarbonitrile (**8b**): Brownish crystals from dioxane, yield (95 %, 2.07 g); mp 218-220 °C; IR (cm⁻¹): 3348, 3302 (NH₂), 3137 (NH) and 2223 (CN); MS m/z (M)⁺ = 218; ¹H-NMR: $\delta = 6.40$ (s, 2H, NH₂), 7.53 (d, 2H, $J = 8.4$ Hz, arom-H), 7.80 (d, 2H, $J = 8.4$ Hz, arom-H), 12.06 (br s, 1H, NH); Anal. calcd. for C₁₀H₇ClN₄: (218): C, 54.93; H, 3.23; N, 25.62. Found: C, 55.07; H, 3.46; N, 25.54.

3-Amino-5-(2-thienyl)-1H-4-pyrazolecarbonitrile (**8c**): Beige crystals from *n*-propanol, yield (93 %, 1.76 g); mp 238-240 °C; IR (cm⁻¹): 3325, 3298 (NH₂), 3177 (NH) and 2228 (CN); MS m/z (M)⁺ = 190; ¹H-NMR: $\delta = 6.38$ (s, 2H, NH₂), 7.14 (t, 1H, $J = 4.4$ Hz, thienyl H-4), 7.70 (d, 1H, $J = 4.4$ Hz, thienyl H-3), 7.93 (d, 1H, $J = 4.2$ Hz, thienyl H-2), 12.00 (br s, 1H, NH); Anal. calcd. for C₈H₆N₄S: (190.23): C, 50.51; H, 3.18; N, 29.45; S, 16.86. Found: C, 50.63; H, 3.02; N, 29.57; S, 17.02.

Reaction of **8a-c** with enaminone **2c** and with enaminonitrile **9**

Procedure A: a mixture of each of compound **8a-c** (10 mmol) and each of **2c** or **9** (10 mmol) was heated under reflux in AcOH (15 mL) for 4h, during which time a precipitate is formed. The reaction mixture was filtered off and recrystallized from acetone.

Procedure B: a mixture of each of compound **8a-c** (10 mmol) and each of **2c** or **9** (10 mmol) was dissolved in ethanol (2 mL) in a small beaker. The reaction mixture was dried in air and the beaker was put in a domestic microwave oven 290 W and irradiate for 15 min. The progress of the reaction was

monitored every 3 min. The product was extracted with acetone (2 x 10 mL). The solvent was removed by distillation under reduced pressure to obtain the crude product that was further recrystallized from the appropriate solvent.

2-Phenyl-7-(2-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (12a): Yellow crystals from acetone, yield (89 %, 2.68 g); mp 237-239 °C; IR (cm⁻¹): 2222 (CN); MS m/z (M)⁺ = 302; ¹H-NMR: δ = 7.45 (t, 1H, *J* = 4.2 Hz, thienyl H-4), 7.62-7.70 (m, 3H, arom. H), 8.06 (d, 1H, *J* = 4.8 Hz, H-6), 8.20 (d, 2H, *J* = 8.0 Hz, arom. H), 8.24 (d, 1H, *J* = 4.2 Hz, thienyl H-3), 8.63 (d, 1H, *J* = 4.2 Hz, thienyl H-5), 8.82 (d, 1H, *J* = 4.8 Hz, H-5); Anal. calcd. for C₁₇H₁₀N₄S: (302.35): C, 67.53; H, 3.33; N, 18.53; S, 10.61. Found: C, 67.64; H, 3.47; N, 18.47; S, 10.43.

2-(4-Chlorophenyl)-7-(2-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (12b): Brownish red crystals from ethanol, yield (86 %, 2.88 g); mp 252-254 °C; IR (cm⁻¹): 2220 (CN); MS m/z (M)⁺ = 336; ¹H-NMR: δ = 7.36 (t, 1H, *J* = 4.2 Hz, thienyl H-4), 7.66 (d, 2H, *J* = 6.6 Hz, arom. H), 7.99 (d, 1H, *J* = 4.8 Hz, H-6), 8.12 (d, 2H, *J* = 6.6 Hz, arom. H), 8.16 (d, 1H, *J* = 4.2 Hz, thienyl H-3), 8.54 (d, 1H, *J* = 4.2 Hz, thienyl H-5), 8.74 (d, 1H, *J* = 4.8 Hz, H-5); Anal. calcd. for C₁₇H₉ClN₄S: (336.8): C, 60.62; H, 2.69; N, 16.64; S, 9.52. Found: C, 60.32; H, 3.07; N, 16.87; S, 9.64.

2,7-Di(2-thienyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (12c): Beige crystals from acetone, yield (88 %, 2.71 g); mp 251-253 °C; IR (cm⁻¹): 2222 (CN); MS m/z (M)⁺ = 308; ¹H-NMR: δ = 7.34 (t, 1H, *J* = 4.8 Hz, thienyl H-4), 7.45 (t, 1H, *J* = 4.8 Hz, thienyl H-4), 7.91 (d, 1H, *J* = 4.8 Hz, thienyl H-3), 7.96 (d, 1H, *J* = 4.8 Hz, thienyl H-3), 8.03 (d, 1H, *J* = 5.2 Hz, H-6), 8.25 (d, 1H, *J* = 4.8 Hz, thienyl H-5), 8.60 (d, 1H, *J* = 4.8 Hz, thienyl H-5), 8.79 (d, 1H, *J* = 5.2 Hz, H-5); Anal. calcd. for C₁₅H₈N₄S₂: (308.38): C, 58.42; H, 2.61; N, 18.17; S, 20.80. Found: C, 58.12; H, 2.67; N, 18.09; S, 20.63.

2-Phenyl-5-(2-thienyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (15a): Grey crystals from acetone, yield (88 %, 2.87 g); mp 291-293 °C; IR (cm⁻¹): 2226 (CN); MS m/z (M)⁺ = 327; ¹H-NMR: δ = 7.46 (t, 1H, *J* = 4.2 Hz, thienyl H-4), 7.56-7.60 (m, 3H, arom. H), 8.12 (d, 2H, *J* = 8.2 Hz, arom. H), 8.39 (d, 1H, *J* = 4.2 Hz, thienyl H-3), 8.67 (d, 1H, *J* = 4.2 Hz, thienyl H-5), 9.09 (s, 1H, H-7); Anal. calcd. for C₁₇H₁₀N₄S: (327.36): C, 66.04; H, 2.77; N, 21.39; S, 9.79. Found: C, 66.25; H, 2.96; N, 21.17; S, 10.03.

2-(4-Chlorophenyl)-5-(2-thienyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (15b): Brown crystals from acetone, yield (85 %, 3.06 g); mp 294-295 °C; IR (cm⁻¹): 2230 (CN); MS m/z (M)⁺ = 361; ¹H-NMR: δ = 7.46 (t, 1H, *J* = 4.2 Hz, thienyl H-4), 7.67 (d, 2H, *J* = 8.2 Hz, arom. H), 8.08 (d, 2H, *J* = 8.2 Hz, arom. H), 8.39 (d, 1H, *J* = 4.2 Hz, thienyl H-3), 8.65 (d, 1H, *J* = 4.2 Hz, thienyl H-5), 9.08 (s, 1H, H-7); Anal. calcd. for C₁₇H₉ClN₄S: (361.81): C, 59.75; H, 2.23; N, 19.36; S, 8.86. Found: C, 59.46; H, 2.49; N, 19.19; S, 8.82.

2,5-Di(2-thienyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile 15c: Brown crystals from acetone, yield (87 %, 2.89 g); mp 303-304 °C; IR (cm⁻¹): 2227 (CN); MS m/z (M)⁺ = 333; ¹H-NMR: δ = 7.27 (t, 1H, *J* = 4.8 Hz, thienyl H-4), 7.45 (t, 1H, *J* = 4.8 Hz, thienyl H-4), 7.87 (d, 1H, *J* = 4.8 Hz, thienyl H-3),

7.92 (d, 1H, $J = 4.8$ Hz, thienyl H-3), 8.40 (d, 1H, $J = 4.8$ Hz, thienyl H-5), 8.63 (d, 1H, $J = 4.8$ Hz, thienyl H-5), 9.06 (s, 1H, H-7); Anal. calcd. for $C_{15}H_8N_4S_2$: (333.39): C, 57.64; H, 2.12; N, 21.01; S, 19.24. Found: C, 57.42; H, 2.43; N, 20.85; S, 19.57.

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Sample Availability: Samples of the compounds **8a-c**, **12a-c** and **15a-c** are available from authors.

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