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β-Amino-β-(pyrid-4-yl)acrylonitrile in heterocyclic synthesis: synthesis of some new pyridine, pyridone, pyrazole, thiophene, fused pyrimidine and triazine derivatives

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Abstract—β-Amino-β-(pyrid-4-yl)acrylonitrile reacts with various types of reagents with variable molar ratios under different conditions to yield pyridine derivatives and condensed heterocyclic compounds containing a pyridyl moiety.

1. Introduction

Substituted pyridines and condensed pyridines are important as pharmaceuticals and agrochemicals,[1–4] and some 2-pyridone derivatives are also of considerable biological importance as cardiotonic agents such as milirinone[5] (Fig. 1) and as potential HIV-1 specific transcriptase inhibitors.[5,6] In continuation of previous work in developing syntheses of polyfunctionally substituted heteroaromatics,[7–10] we report here several new approaches to these derivatives using β-amino-β-(pyrid-4-yl)acrylonitrile **1** as a precursor.

2. Results and discussion

The enaminonitrile **1** can be readily prepared and obtained in excellent yield by reaction of acetonitrile with 4-cyanopyridine in the presence of potassium-*t*-butoxide.[11] Now we have found that compound **1** is an attractive starting material for the preparation of pyridine derivatives. Thus, the reaction of **1** with different types of aldehydes in AcOH under reflux yielded 2:1 adducts formulated as pyridines **5a–d** in good yield which are believed to be formed via initial condensation of **1** with appropriate aldehydes **2a–f** to form the intermediates **3** which in turn react with another mole of **1** to form intermediate diamines **4** which cyclized via loss of NH_3 and auto aromatization under the reaction conditions. The structures of **5** were confirmed based on the elemental analyses and spectral data. Thus, the IR spectrum showed the absence of NH stretching and the presence of a bands at 2208 cm^{-1} for the cyano groups. The ^1H NMR spectrum of **5d** revealed the presence of signals at 3.74–3.88 ppm corresponding to 3-OCH_3 groups and the absence of the signal of the 4*H*-pyridine at 4.91. In addition, the spectrum showed the presence of a singlet signal at δ 7.27 corresponding to 2*H*-aromatic and two doublet signals at 8.05 and 8.91 corresponding to 3,5*H*- and 2,6*H*-pyridyl protons, respectively. The mass spectrum of **5d** is in accordance with the proposed structure which showed a molecular ion peak *m*/*z*=449 (100%) corresponding to the molecular formula $C_{26}H_{19}N_5O_3$. Similarly aldehydes **2a–c,e,f** reacted with **1** to afford pyridine derivatives **5a–c,e,f** (Scheme 1).

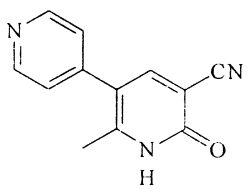

Figure 1.

The efficiency of the above reactions prompted us to extend this procedure to the synthesis of compounds containing two pyridine units attached to a benzene ring. The reaction of **1** with terephthalaldehyde in a 4:1 molar ratio carried out in AcOH afforded the desired 1,4-bis(pyridyl)-benzene derivative **6** in a moderate (52%) yield. Its structure was confirmed by analytical and spectroscopic data which are similar to those of **5a** (Scheme 1).

Also, reaction of **1** with salicylaldehyde under the previous conditions gave a 1:2 adduct which is formulated as

Keywords: β-amino-β-(pyrid-4-yl)acrylonitrile; enaminone; thiophene; ethyl cyanoacetate.

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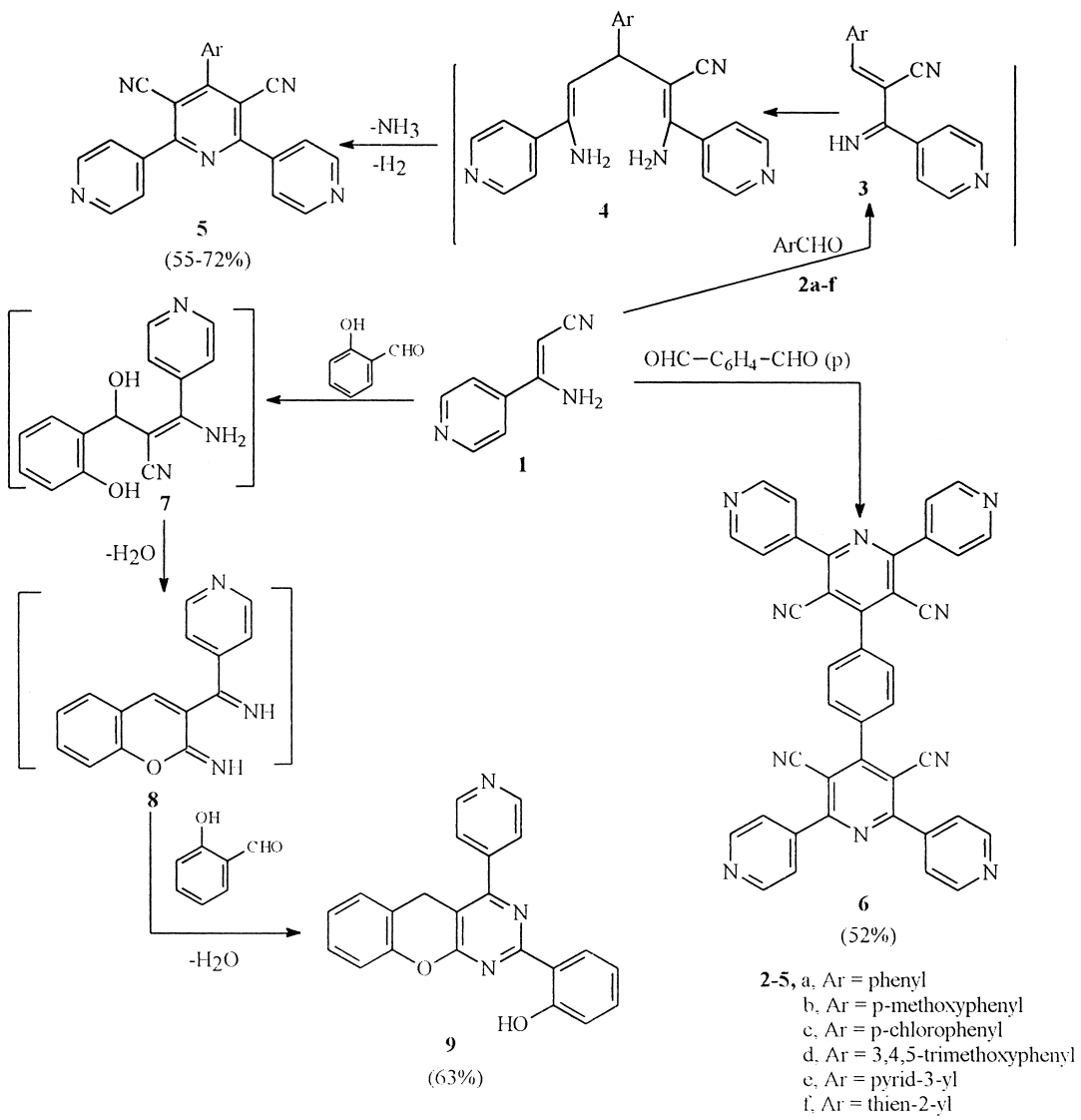
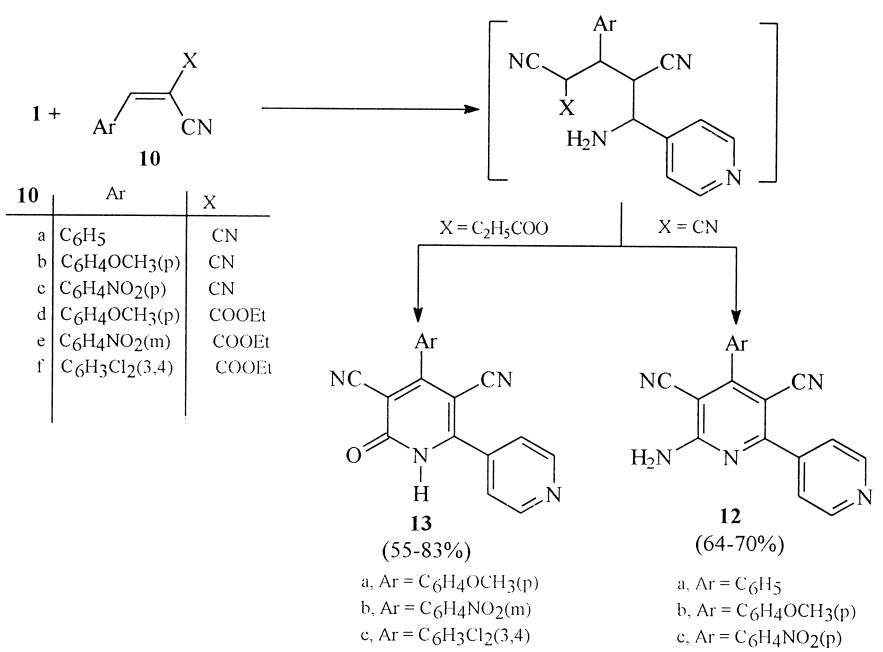
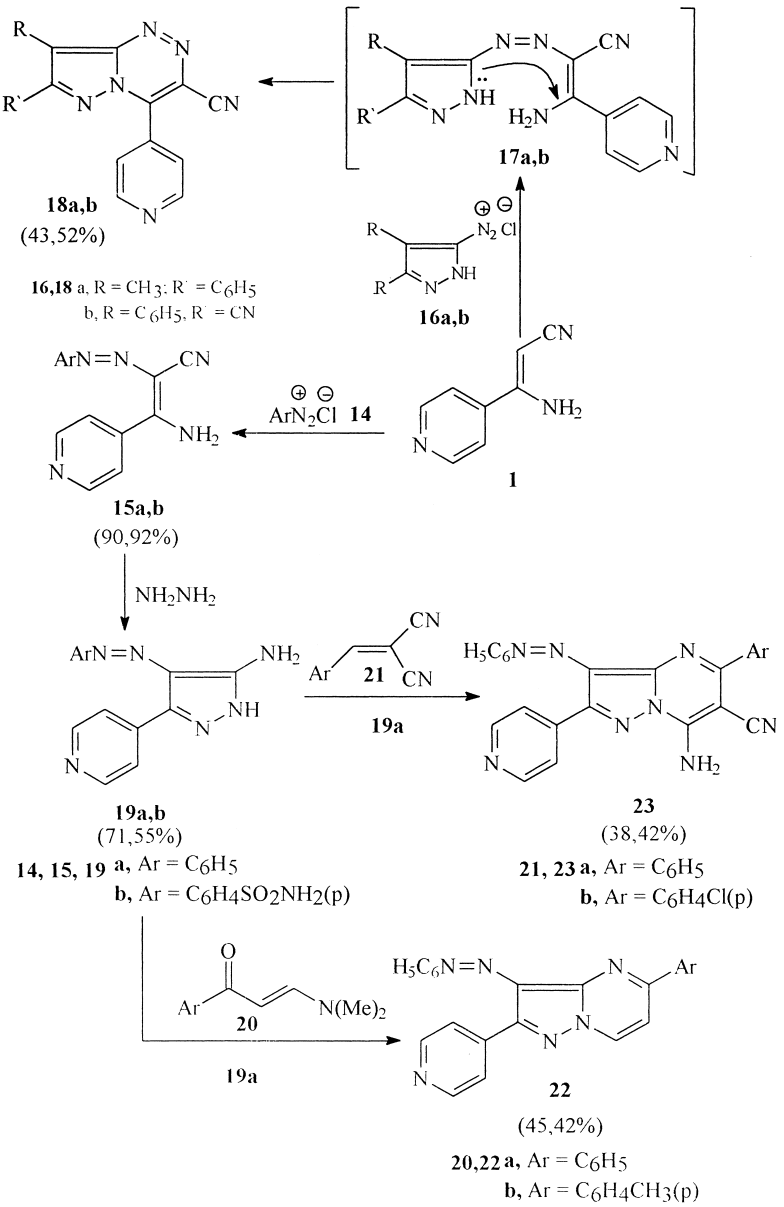


Scheme 1.



10	Ar	X
a	C_6H_5	CN
b	$C_6H_4OCH_3$(p)	CN
c	$C_6H_4NO_2$(p)	CN
d	$C_6H_4OCH_3$(p)	COOEt
e	$C_6H_4NO_2$(m)	COOEt
f	$C_6H_3Cl_2$(3,4)	COOEt

Scheme 2.



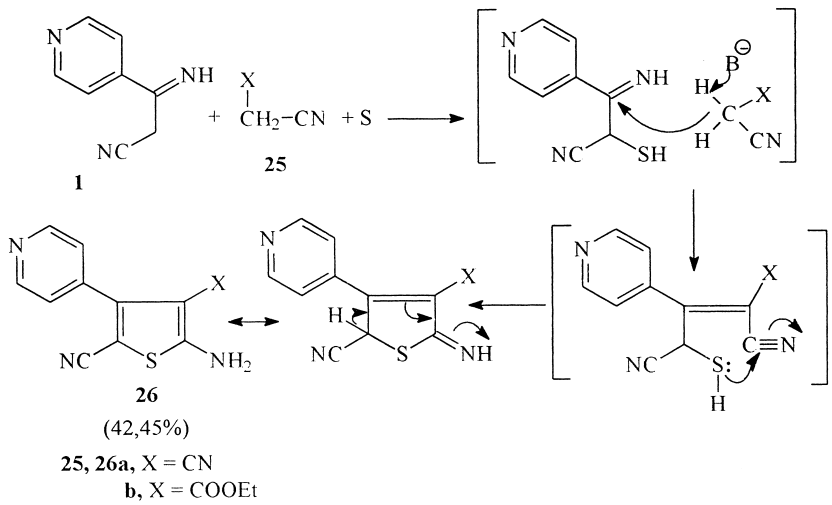
Scheme 3.

2-(*o*-hydroxyphenyl)-4-(pyrid-4-yl)benzo[5′.6′]-4*H*-pyrano-[2,3-*d*]pyrimidine **9**. Compound **9** is assumed to be formed via initial addition of salicylaldehyde with elimination of 1 mol of water to form the non-isolable intermediates **7** and **8**. The latter intermediate **8** in turn, reacted with another molecule of salicyaldehyde giving the cyclized product **9**. The structure of **9** was established based on its spectral data. Thus, the IR spectrum (KBr) showed stretching bands at 3400 cm^{-1} for OH and 1620 cm^{-1} for C=N groups. The ^1H NMR spectrum revealed the presence of a singlet at δ=4.95 ppm corresponding to 2*H* of 4*H* pyran, a multiplet at δ=7.11–7.55 ppm due to the aromatic protons, doublets at 8.43, 8.47 and 8.85 corresponding to the pyridyl protons and a singlet at 12.79 corresponding to the phenolic OH. Also, its mass spectrum revealed M^+ at *m/z*=353 (100%) corresponding to the molecular formula $C_{22}H_{15}N_3O_2$.

Next we investigated the applicability and synthetic potency of **1** in a convenient route to polyfunctionally substituted pyridine derivatives of an expected wide spectrum of bioresponce.[5,6] Thus, compound **1** reacted with an equimolar amount of α-cinnamonitriles **10a–f** to provide pyridine and pyridinone derivatives **12** and **13**, respectively, in acceptable yields.

Formation of **12** and **13** is assumed to proceed via an acyclic intermediate **11** followed by intramolecular cyclization and spontaneous autooxidation under the reaction conditions in the case of **12** and elimination of ethanol in the case of **13** (Scheme 2). The structure of **12** and **13** were established on the basis of elemental and spectroscopic studies.

Work was further extended to study the behavior of **1** towards the action of aryl and heterocyclic diazonium chloride.[12] Thus, compound **1** readily coupled with aromatic diazonium salts **14** yielding the corresponding coupling



Scheme 4.

products that were assigned as the arylazo-enaminonitrile derivatives **15** based on elemental analysis and spectral data. But in the case of heterocyclic diazonium chlorides **16** the pyrazolo[1,5-*c*][1,2,4]triazine derivatives **18a**,**b** were obtained via the non-isolable intermediates **17** by loss of 1 mol of ammonia. Similar cyclization reactions to form pyrazolotriazine have been previously reported.[13–15] Compound **15** reacted with hydrazine hydrate to afford the aminopyrazole derivatives **19a**,**b**. Compound **19a** reacted easily with an equimolar amount of both enaminones **20a**,**b** and enaminonitrile **21a**,**b** in ethanol with a catalytic amount of piperidine to provide pyrazolo[1,5-*a*]-pyrimidine derivatives[7,16] **22a**,**b** and **23a**,**b**, respectively (Scheme 3).

Moreover, the behavior of **1** towards the active methylene-nitriles reagents was also investigated.[15,17] Thus a mixture of **1** and methylenenitrile **25a** or **b** and elemental sulfur in refluxing dioxane in the presence of a catalytic amount of piperidine enabled the synthesis of 4-(5-amino-thiophen-3-yl)pyridine derivatives **26a**,**b**, in excellent yields. It is believed that the reaction proceeds via the mechanistic path illustrated in Scheme 4. The validity of structures **26a**,**b** were deduced from their correct elemental analysis and compatible spectral data.

3. Conclusion

In conclusion, we have investigated the applicability and synthetic potency of β-amino-β-(pyrid-4-yl)acrylonitrile in a convenient route to synthesize with a facile and simple reaction conditions polyfunctionally substituted 4,2′:6′,4″-terpyridine derivatives **5** and 4,2′-bispyridines **12** and **13** in acceptable yield. Also, the behavior of **1** towards some aryl (heterocyclic) diazonium chlorides was studied for preparing condensed heterocyclic compounds containing pyridine moiety such as pyrazolo[5,1-*c*][1,2,4]triazine derivatives **18**, pyrazolo[1,5-*a*]pyrimidines **22** and **23**. Similarly, the reactivity of **1** towards some active methylenenitriles was studied to synthesize thiophene derivatives **26**.

4. Experimental

Melting points are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8201 PC spectrophotometer. ^{1}H NMR spectra were obtained on a Varian Germini 200 MHz spectrometer in DMSO-d_6 as solvent and TMS as an internal reference Mass spectra were performed on a Shimadzu GCMS-QP-1000 EX using the direct inlet system and EI+QI MSLMRUPLR Microanalysis was performed by the Microanalytical Unit at Cairo University. Thin layer chromatography was carried out on 5×20 cm plates coated with silica gel GF 254 type 60, mesh size 50–250. Compounds **1**[11] and **19**[10] were prepared according to the methods reported in the literature.[10,11]

4.1. Preparation of β-amino-β-(pyrid-4-yl)acrylonitrile 1

The title compound was prepared according to reported literature.[11] (0.91 g, 63%) as colorless solid, mp 202°C. [Found: C, 66.20; H, 4.82; N, 28.96. $C_8H_7N_3$ requires C, 66.20; H, 4.80; N, 28.20; ν_{max} [KBr] 3335, 2193 cm^{-1}; *m/z* 99 (34), 117 (100), 145 (49), found 145.14. $C_8H_7N_3$ requires 145.14.

4.2. Preparation of pyridine derivatives 5a–f, 6 and 9

A solution of **1** (2.9 g, 0.02 mol) in glacial acetic acid (30 mL) was treated with the appropriate aromatic or heterocyclic aldehydes **2a–f** (0.01 mol). The reaction mixture was heated under reflux for 5–8 h and the solvent was then evaporated in vacuo. The residue was triturated with water, the solid product so formed was collected by filtration and crystallized from ethanol.

4.2.1. 3,5-Dicyano-4-phenyl-2,2′:6′,4″-terpyridine (5a). The title compound was obtained as white solid (2.58 g, 72%), mp 256°C. [Found: C, 76.80; H, 3.60; N, 19.40. $C_{23}H_{13}N_5$ requires C, 76.86; H, 3.64; N, 19.48; ν_{max} [KBr] 3050, 2196, 1585 cm^{-1}; δ_H (DMSO-d_6) 7.01–7.83 (m, 5H, H-Ar), 8.35 (d, 4H, *J*=6.0 Hz, 3,5H-pyridyl), 8.90 (d, 4H, *J*=6.0 Hz, 2,6H-pyridyl).

4.2.2. 3,5-Dicyano-4-(*p*-methoxyphenyl)-2,2′:6′,4″-terpyridine (5b). The title compound was obtained as pale yellow solid (2.41 g, 62%), mp 247°C. [Found: C, 74.10; H, 3.80; N, 17.80. $C_{24}H_{15}N_5O$ requires C, 74.02; H, 3.88; N, 17.98; ν_{max} [KBr] 2939, 2210 cm^{-1}; δ_H (DMSO-d_6) 3.71 (s, 3H, OCH_3), 7.01–7.73 (m, 4H, H-Ar), 8.31 (d, 4H, *J*=7.0 Hz, 3,5H-pyridyl), 8.83 (d, 4H, *J*=7.0 Hz, 2,6H-pyridyl).

4.2.3. 3,5-Dicyano-4-(*p*-chlorophenyl)-2,2′:6′,4″-terpyridine (5c). The title compound was obtained as colorless solid (2.36 g, 60%), mp 280°C. [Found: C, 70.20; H, 3.10; N, 18.10, Cl, 9.0. $C_{23}H_{12}N_5Cl$ requires C, 70.16; H, 3.07, N, 17.78, Cl, 9.0; ν_{max} [KBr] 3045, 2196 cm^{-1}; δ_H (DMSO-d_6) 7.01–7.83 (m, 4H, H-Ar), 8.21 (d, 4H, *J*=8.0 Hz, 3,5-H-pyridyl), 8.63 (d, 4H, *J*=8.0 Hz, 2,6-H-pyridyl); *m/z* 51 (35), 178 (28), 353 (62), 348 (42), 393 (100), 394 (65), found 393.32 $C_{23}H_{12}N_5Cl$ requires 393.32.

4.2.4. 3,5-Dicyano-4-(3,4,5-trimethoxyphenyl)-2,2′:6′,4″-terpyridine (5d). The title compound was obtained as yellow solid (2.46 g, 55%), mp 258°C. [Found: C, 69.50; H, 4.30; N, 15.80. $C_{26}H_{19}N_5O_3$ requires C, 69.47; H, 4.26; N, 15.58; ν_{max} [KBr] 2949, 2208 cm^{-1}; δ_H (DMSO-d_6) 3.74–3.88 (m, 9H, $3OCH_3$), 7.27 (s, 2H, H-Ar), 8.05 (d, 4H, *J*=5.8 Hz, 3,5H-pyridyl), 8.91 (d, 4H, *J*=5.6 Hz, 2,6H-pyridyl); *m/z* 51 (25), 284 (100), 358 (30), 449 (98), found 449.46 $C_{26}H_{19}N_5O_3$ requires 449.46.

4.2.5. 3,5-Dicyano-4-(pyrid-3-yl)-2,2′:6′,4″-terpyridine (5e). The title compound was obtained as pale yellow solid (2.08 g, 58%), mp 282°C. [Found: C, 73.20; H, 3.50; N, 24.00. $C_{22}H_{12}N_6$ requires C, 73.32; H, 3.35; N, 23.32; ν_{max} [KBr] 3038, 2225 cm^{-1}; δ_H (DMSO-d_6) 5.6 (br, 1H, 4-H pyridyl), 8.05 (d, 5H, *J*=6.0 Hz, 3,5H-pyridyl), 8.91 (d, 6H, *J*=5.8 Hz, 2,6H-pyridyl).

4.2.6. 3,5-Dicyano-4-(thien-2-yl)-2,2′:6′,4″-terpyridine (5f). The title compound was obtained as yellowish green solid (2.26 g, 62%), mp 290°C. [Found: C, 69.10; H, 3.20; N, 19.30; S, 9.00. $C_{21}H_{11}N_5S$ requires C, 69.02; H, 3.03; N, 19.16; S, 8.77; ν_{max} [KBr] 3038, 2190 cm^{-1}; δ_H (DMSO-d_6) 7.2–7.3 (m, 1H, 4-H-theinyl), 7.3–7.83 (m, 2H, 3,5-H-theinyl), 8.32 (d, 4H, *J*=7.0 Hz, 3,5-H-pyridyl), 8.69 (d, 4H, *J*=7.0 Hz, 2,6-H-pyridyl); *m/z* 51 (30), 282 (100), 305 (48), 365 (40), found 365.40 $C_{21}H_{11}N_5S$ requires 365.40.

4.2.7. Bis(3,5-dicyano-2,2′:6′,4″-terpyrid-4-yl)benzene (6). The title compound was obtained as yellow solid (3.32 g, 52%), mp 265°C. [Found: C, 75.10; H, 3.30; N, 21.70. $C_{40}H_{20}N_{10}$ requires C, 74.99; H, 3.14; N, 21.86; ν_{max} [KBr] 3042, 2225 cm^{-1}; δ_H (DMSO-d_6) 7.01–7.50 (4H, H-Ar), 8.02 (d, 8H, *J*=5.8 Hz, 3,5-H-pyridyl), 8.815 (d, 8H, *J*=6.0 Hz, 2,6-H-pyridyl).

4.2.8. 2-(*o*-Hydroxyphenyl)-4-(pyrid-4-yl)benzo[5′,6′]-4*H*-pyrano[2,3-*d*]pyrimidine (9). The title compound was obtained as pale violet solid (2.22 g, 63%), mp 245°C. [Found: C, 74.60; H, 4.30; N, 11.70. $C_{22}H_{15}N_3O_2$ requires C, 74.77; H, 4.27; N, 11.89; ν_{max} [KBr] 3400, 3030, 2927, 1620 cm^{-1}; δ_H (DMSO-d_6) 4.95 (s, 2H, 4H-pyron), 7.11–7.55 (m, 8H, H-Ar), 8.45 (d, 2H, *J*=8.0 Hz, 3,5-H-pyridyl), 8.85 (br, 2H, 2,6-H-pyridyl), 12.79 (s, 1H, OH); *m/z* 51 (25), 28 (25), 130 (40), 235 (20), 353 (100), found 353.36 $C_{22}H_{15}N_3O_2$ requires 353.36.

4.3. Preparation of pyridine derivatives 12a–c and 13a–c

A solution of **1** (0.725 g, 0.005 mol) in absolute ethanol (30 mL) was treated with the appropriate cinnamonitrile derivatives **10a–f** (0.005 mol) and a few drops of triethylamine. The reaction mixture was refluxed for 7–10 h and the solvent was then evaporated in vacuo. The residue was triturated with cold water and neutralized with dilute hydrochloric acid. The solid obtained was collected by filtration and crystallized from ethanol.

4.3.1. 6-Amino-3,5-dicyano-4-phenyl-2′,4-bispyridine (12a). The title compound was obtained as pale violet solid (1.83 g, 65%), mp 270°C. [Found: C, 72.90; H, 3.80; N, 23.40. $C_{18}H_{11}N_5$ requires C, 72.71; H, 3.72; N, 23.55; ν_{max} [KBr] 3320, 3290, 2219 cm^{-1}; δ_H (DMSO-d_6) 7.10 (s, 2H, NH_2), 7.43–7.89 (m, 5H, H-Ar), 8.51 (d, 2H, *J*=6.0 Hz, 3,5H-pyridyl), 8.93 (d, 2H, *J*=6.0 Hz, 2,6H-pyridyl); *m/z* 51 (25), 158 (30), 250 (50), 297 (100), found 297.30 $C_{18}H_{11}N_5$ requires 297.30.

4.3.2. 6-Amino-3,5-dicyano-4-(*p*-methoxyphenyl)-2′,4-bispyridine (12b). The title compound was obtained as pale yellow solid (2.09 g, 64%), mp 260°C. [Found: C, 70.10; H, 3.90; N, 22.00. $C_{19}H_{13}N_5O$ requires C, 69.71; H, 4.00; N, 21.39; ν_{max} [KBr] 3301, 3191, 2214, 1630 cm^{-1}; δ_H (DMSO-d_6) 3.87 (s, 3H, OCH_3), 7.14 (b, 2H, NH_2), 7.59–7.79 (d, 4H, Ar-H), 8.35 (b, 2H, 3,5-H-pyridyl), 8.79 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl). *m/z* 51 (35), 142 (20), 270 (40), 296 (80), 327 (100), found 327.33 $C_{19}H_{13}N_5O$ requires 327.33.

4.3.3. 6-Amino-3,5-dicyano-4-(*p*-nitrophenyl)-2-(pyrid-4-yl)pyridine (12c). The title compound was obtained as pale brown solid (2.39 g, 70%), mp 265°C. [Found: C, 63.40; H, 3.10; N, 24.90. $C_{18}H_{10}N_6O_2$ requires C, 63.15; H, 2.94; N, 24.55; ν_{max} [KBr] 3360, 3310, 2214 cm^{-1}; δ_H (DMSO-d_6) 6.93–7.71 (m, 6H, 4H-Ar+NH_2), 8.23 (d, 2H, *J*=7.0 Hz, 3,5-H-pyridyl), 8.64 (d, 2H, *J*=7.0 Hz, 2,6-H-pyridyl); *m/z* 51 (35), 184 (50), 276 (63), 342 (100), found 342.31 $C_{18}H_{10}N_6O_2$ requires 342.31.

4.3.4. 3,5-Dicyano-1*H*-4-(*p*-methoxyphenyl)-2′,4-bispyridin-6-one (13a). The title compound was obtained as deep yellow solid (1.80 g, 55%), mp 263°C. [Found: C, 69.60; H, 3.70; N, 17.10. $C_{19}H_{12}N_4O_2$ requires C, 69.50; H, 3.68; N, 17.06; ν_{max} [KBr] 3050, 3210, 2218, 1710 cm^{-1}; δ_H (DMSO-d_6) 3.83 (s, 3H, OCH_3), 7.13–7.89 (m, 4H, H-Ar), 8.51 (d, 2H, *J*=6.0 Hz, 3,5H-pyridyl), 8.91 (d, 2H, *J*=6.0 Hz, 2,6H-pyridyl), 9.1 (s, 1H, NH); *m/z* 51 (25), 118 (30), 218 (40), 256 (100), 328 (50), found 328.31 $C_{19}H_{12}N_4O_2$ requires 328.31.

4.3.5. 3,5-Dicyano-1*H*-4-(*p*-nitrophenyl)-2′,4-bispyridin-6-one (13b). The title compound was obtained as pale yellow solid (2.05 g, 60%), mp 248°C. [Found: C, 63.10; H, 2.70; N, 20.50. $C_{18}H_9N_5O_3$ requires C, 62.97; H, 2.64; N, 20.39; ν_{max} [KBr] 3068, 3230, 2218, 1716 cm^{-1}; δ_H (DMSO-d_6) 7.78–8.08 (m, 4H, H-Ar), 8.49 (dd, 2H, *J*=8.0 Hz, 3,5-H-pyridyl), 8.84 (dd, 2H, *J*=8.0 Hz,

2,6-H-pyridyl), 8.93 (s, 1H, NH) *m/z* 51 (50), 106 (15), 215 (22), 297 (100), 334 (50), 343 (80), found 343.29 $C_{18}H_9N_5O_3$ requires 343.29.

4.3.6. 3,5-Dicyano-1*H*-4-(3,4-dichlorophenyl)-2′,4-bispyridin-6-one (13c). The title compound was obtained as pale yellow solid (3.04 g, 83%), mp 238°C. [Found: C, 59.10; H, 2.30; N, 15.60; Cl, 20.10. $C_{18}H_8N_4OCl_2$ requires C, 58.88, H, 2.19; N, 15.25, Cl, 19.70; ν_{max} [KBr] 3190, 3060, 2218, 1714 cm^{-1}, δ_H (DMSO-d_6) 7.60–7.76 (m, 3H, H-Ar), 7.81 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.89 (dd, 2H, *J*=6 Hz, 2,6-H-pyridyl), 8.91 (s, 1H, NH). *m/z* 51 (30), 148 (35), 265 (24), 367 (100), found 367.17 $C_{18}H_8N_4OCl_2$ requires 367.17.

4.4. Preparation of arylazo enaminonitrile derivatives 15a,b and pyrazolo[5,1-*c*][1,2,4]triazine derivatives 18a,b

A solution of diazotized aromatic and heterocyclic amines **14a**,**b** and **16a**,**b**, respectively [prepared from the appropriate amines (0.01 mol) in hydrochloric acid and sodium nitrite (0.01 mol)] was added to enaminonitrile **1** (1.45 g, 0.01 mol) in ethanol (50 mL) containing 1–2 g of sodium acetate. The reaction mixture was then stirred in an ice bath for 1–2 h. The solid so formed, was collected by filtration and washed several times with water and recrystallized from ethanol.

4.4.1. 3-Amino-2-phenylazo-3-(pyrid-4-yl)acrylonitrile (15a). The title compound was obtained as yellow solid (2.24 g, 90%), mp 226°C. [Found: C, 67.50; H, 4.50; N, 28.20. $C_{14}H_{11}N_5$ requires C, 67.45; H, 4.44; N, 28.08; ν_{max} [KBr] 3292, 3226, 2215, 1625 cm^{-1}; δ_H (DMSO-d_6) 6.05 (s, 2H, NH_2), 6.93–7.81 (m, 5H, H-Ar), 8.33 (d, 2H, *J*=8.0 Hz, 3,5-H-pyridyl), 8.78 (d, 2H, *J*=8.0 Hz, 2,6-H-pyridyl); *m/z* 51 (75), 77 (100), 172 (25), 249 (48), found 249.26 $C_{14}H_{11}N_5$ requires 249.26.

4.4.2. 3-Amino-2-(*p*-sulfonamidophenylazo)-3-(pryid-4-yl)acrylonitrile (15b). The title compound was obtained as orange solid (3.01 g, 92%), mp 240°C. [Found: C, 51.30; H, 3.70; N, 25.70; S, 10.00. $C_{14}H_{12}N_6O_2S$ requires C, 51.21; H, 3.68; N, 25.59; S, 9.76; ν_{max} [KBr] 3295–3226, 2214, 1652 cm^{-1}; δ_H (DMSO-d_6) 6.10 (s, 2H, NH_2). 7.10–7.68 (m, 6H, 4H-Ar+NH_2), 8.05 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.92 (d, 2H, *J*=5.8 Hz, 2,6-H-pyridyl).

4.4.3. 3-Cyano-8-methyl-7-phenyl-4-(pyrid-4-yl)pyrazolo[5,1-*c*][1,2,4]triazine (18a). The title compound was obtained as brown solid (1.62 g, 52%), mp 208°C. [Found: C, 69.40; H, 3.70; N, 26.90. $C_{18}H_{12}N_6$ requires C, 69.22; H, 3.87; N, 26.90, ν_{max} [KBr] 3035, 2973, 2220 cm^{-1}; δ_H (DMSO-d_6) 3.10 (s, 3H, CH_3), 7.10–7.56 (m, 5H, H-Ar), 8.12 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.85 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl), *m/z* 51 (30), 148 (22), 228 (40), 312 (100), found 312.32 $C_{18}H_{12}N_6$ requires 312.32.

4.4.4. 3,7-Dicyano-8-phenyl-4-(pyrid-4-yl)pyrazolo[5,1-*c*][1,2,4]triazine (18b). The title compound was obtained as brown solid (1.38 g, 43%), mp 284°C. [Found: C, 67.10; H, 2.80; N, 30.50. $C_{18}H_9N_7$ requires C, 66.86; H, 2.80; N, 30.32, ν_{max} [KBr] 3045, 2220, 2192 cm^{-1}, δ_H (DMSO-d_6) 7.23–7.71 (m, 5H, H-Ar), 8.22 (d, 2H, *J*=5.4 Hz, 3,5-H-pyridyl), 8.87 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl).

4.4.5. Compound 19a. Compound **19a** was prepared according to reported literature.[10]

The title compound was obtained as pale yellow solid (1.87 g, 71%), mp 295°C. [Found: C, 64.10; H, 4.60; N, 31.90. $C_{14}H_{12}N_6$ requires C, 63.67; H, 4.57; N, 31.79; ν_{max} [KBr] 3401, 3360, 3100, 1634 cm^{-1}; δ_H (DMSO-d_6) 7.13–7.93 (m, 7H, NH_2, 5H-Ar), 8.31 (d, 2H, *J*=6.0 Hz, 3,5H-pyridyl), 8.94 (d, 2H, *J*=6.0 Hz, 2,6H-pyridyl), 12.3 (br, 1H, NH); *m/z* 51 (70), 148 (60), 210 (25), 264 (100), found 264.28 $C_{14}H_{12}N_6$ requires 264.28.

4.4.6. Compound 19b. Compound **19b** was prepared according to reported literature.[10]

The title compound was obtained as yellow solid (1.88 g, 55%), mp 290°C. [Found: C, 49.30; H, 3.90; N, 28.90; S, 10.00. $C_{14}H_{13}N_7O_2S$ requires C, 48.97; H, 3.81; N, 28.55; S, 9.33; ν_{max} [KBr] 3438, 3301, 3190, 1631 cm^{-1}; δ_H (DMSO-d_6): 7.44–7.94 (m, 8H, 4H-Ar+NH_2), 8.15 (d, 2H, *J*=5.8 Hz, 3,5-H-pyridyl), 8.65 (d, 2H, *J*=5.8 Hz, 2,6-H-pyridyl), 12.50 (br, 1H, NH); *m/z* 51 (60), 131 (75), 184 (100), 265 (25), 343 (60), found 343.35 $C_{14}H_{13}N_7O_2S$ requires 343.35.

4.5. Preparation of pyrazolo [1,5-*a*]pyrimidine derivatives 22a,b

A solution of **19a** (1.32 g, 0.005 mol) and enaminones **20a** or **b** (0.005 mol) in ethanol/acetic acid (1:1) (30 mL) was refluxed for 5–7 h. The solvent was removed by distillation under reduced pressure and the resulting residue was left to cool. The solid precipitate was collected and recrystallized from ethanol.

4.5.1. 2-Phenyl-8-phenylazo-7-(pyrid-4-yl)pyrazolo[1,5-*a*]-pyrimidine (22a). The title compound was obtained as orange solid (1.69 g, 45%), mp 238°C. [Found: C, 73.20; H, 4.40; N, 22.20. $C_{23}H_{16}N_6$ requires C, 73.32; H, 4.25; N, 22.31; ν_{max} [KBr] 3045, 1625 cm^{-1}; δ_H (DMSO-d_6) 7.1–7.81 (m, 12H, 10H-Ar+2H pyrimidine), 8.12 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.92 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl); *m/z* 51 (25), 180 (30), 376 (100), found 376.40 $C_{23}H_{14}N_6$ requires 376.40.

4.5.2. 2-(*p*-Tolyl)-8-phenylazo-7-(pyrid-4-yl)pyrazolo-[1,5-*a*]pyrimidine (22b). The title compound was obtained as orange solid (1.63 g, 42%), mp 247°C. [Found: C, 73.70; H, 4.50; N, 21.40. $C_{24}H_{18}N_6$ requires C, 73.82; H, 4.64; N, 21.52; ν_{max} [KBr] 3035, 1635 cm^{-1}; δ_H (DMSO-d_6) 2.21 (s, 3H, CH_3), 7.01–7.89 (m, 11H, 9H-Ar+2H pyrimidine), 8.21 (d, 2H, *J*=7.0 Hz, 3,5-H-pyridyl), 8.75 (d, 2H, *J*=7.0 Hz, 2,6-H-pyridyl); *m/z* 51 (25), 138 (25), 254 (40), 390 (100), found 390.44 $C_{24}H_{18}N_6$ requires 390.44.

4.6. Preparation of pyrazolo[1,5-*a*]pyrimidine derivatives 23a,b

A suspension of **19a** (1.32 g, 0.005 mol) and the appropriate cinnamonitrile derivatives **21a**,**b** (0.005 mol) in absolute

ethanol (30 mL) and a catalytic amount of piperidine (four drops) were for 4–6 h. The solvent was concentrated under reduced pressure then the reaction mixture was triturated with cold water and the solid obtained was collected and recrystallized from ethanol.

4.6.1. 4-Amino-3-cyano-2-phenyl-8-phenylazo-7-(pyrid-4-yl)pyrazolo[1,5-*a*]pyrimidine (23a). The title compound was obtained as pale brown solid (1.58 g, 38%), mp 310°C. [Found: C, 69.10; H, 3.80; N, 27.30. $C_{24}H_{16}N_8$ requires C, 69.22; H, 3.87; N, 26.90; ν_{max} [KBr] 3313, 3228, 2212, 1644 cm^{-1}; δ_H (DMSO-d_6) 7.10–7.74 (m, 10H, H-Ar), 8.03 (d, 2H, *J*=8 Hz, 3,5-H-pyridyl), 8.41 (s, 2H, NH_2), 8.83 (d, 2H, *J*=8 Hz, 2,6-H-pyridyl); *m/z* 51 (33), 248 (30), 241 (17), 416 (100), found 416.43 $C_{24}H_{16}N_8$ requires 416.43.

4.6.2. 4-Amino-3-cyano-2-(*p*-chlorophenyl)-8-phenylazo-7-(pyrid-4-yl)pyrazolo[1,5-*a*]pyrimidine (23b). The title compound was obtained as brown solid (1.89 g, 42%), mp 322°C. [Found: C, 63.90; H, 3.20; N, 25.30; Cl, 8.10. $C_{24}H_{15}N_8Cl$ requires C, 63.93; H, 3.35; N, 24.85; Cl, 7.86; ν_{max} [KBr] 3320, 3280, 2192, 1635 cm^{-1}; δ_H (DMSO-d_6) 7.10–7.80 (m, 9H, H-Ar), 8.20 (d, 2H, *J*=6.0 Hz, 3,5H-pyridyl), 8.51 (s, 2H, NH_2), 8.91 (d, 2H, *J*=6.0 Hz, 2,6H-pyridyl), *m/z* 51 (40), 153 (30), 245 (40), 314 (20), 451 (100), found 450.88 $C_{24}H_{15}N_8Cl$ requires 450.88.

4.7. Preparation of aminothiophene derivatives 26a,b

To a solution of **1** (1.45 g, 0.01 mol) in dioxane (30 mL) containing (0.2 mL) of piperidine, malononitrile (0.66 g, 0.01 mol) or ethyl cyanoacetate (1.13 g, 0.01 mol) and elemental sulfur (0.32 g, 0.01 mol) were added. The reaction mixture was refluxed for 4–5 h, then poured onto cold water and neutralized by HCl. The solid so formed was collected by filtration and crystallized from ethanol.

4.7.1. 4-[5-Amino-2,4-dicyano(thien-3-yl)pyridine (26a). The title compound was obtained as dark brown solid (0.94 g, 42%), mp 263°C. [Found: C, 58.60; H, 2.80; N, 25.10; S, 14.20. $C_{11}H_6N_4S$ requires C, 58.39; H, 2.66; N, 24.76; S, 13.52; ν_{max} [KBr] 3400, 3315, 2205, 3198 cm^{-1}; δ_H (DMSO-d_6) 6.69 (s, 2H, NH_2), 8.05 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.91 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl); *m/z* 60 (89), 110 (22), 164 (100), 226 (89), found 226.24 $C_{11}H_6N_6S$ requires 226.24.

4.7.2. 4-[Ethyl 5-amino-2-cyano(thien-3-yl)]-4-carboxylatepyridine (26b). The title compound was obtained as dark brown solid (1.22 g, 45%), mp 242°C. [Found: C, 57.10; H, 4.40; N, 16.00; S, 12.10. $C_{13}H_{11}N_5SO_2$ requires C, 56.93; H, 4.37, N, 15.33; S, 11.69, ν_{max} [KBr] 3403, 2204, 1705 cm^{-1}; δ_H (DMSO-d_6) 1.20 (t, 3H, *J*=7 Hz, CH_3), 4.28 (q, 2H, *J*=7 Hz, CH_2), 6.91 (s, 2H, NH_2), 8.49 (d, 2H, *J*=6.0 Hz, 3,5-H-pyridyl), 8.93 (d, 2H, *J*=6.0 Hz, 2,6-H-pyridyl), *m/z*, 51 (20), 115 (30), 165 (100), 288 (30), 273 (15), found 273.30 $C_{13}H_{11}N_3SO_2$ requires 273.30.

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