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SYNTHESIS OF PYRIDINE-2,6-BIS((*E*)-2-BENZYLIDENE-3-OXO-PROPANENITRILE) AND ITS BEHAVIOR TOWARDS NITROGEN BINUCLEOPHILES

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Abstract – Several new pyrazole, isoxazole and pyrimidine derivatives attached to pyridine ring at 2,6-positions have been synthesized by the reactions of the versatile multifunctional unreported pyridine-2,6-bis((*E*)-2-benzylidene-3-oxopropane-nitrie) (**2a**) with several nitrogen binucleophiles. A novel one-pot three-component reaction of an aldehyde, pyridine-2,6-bis(3-oxopropanenitrile) (**1**) and electron-rich heterocyclic amines including [3-phenyl-1*H*-pyrazol-5-amine (**12**) and 2-aminobenzimedazole (**16**)] in DMF have been described.

INTRODUCTION

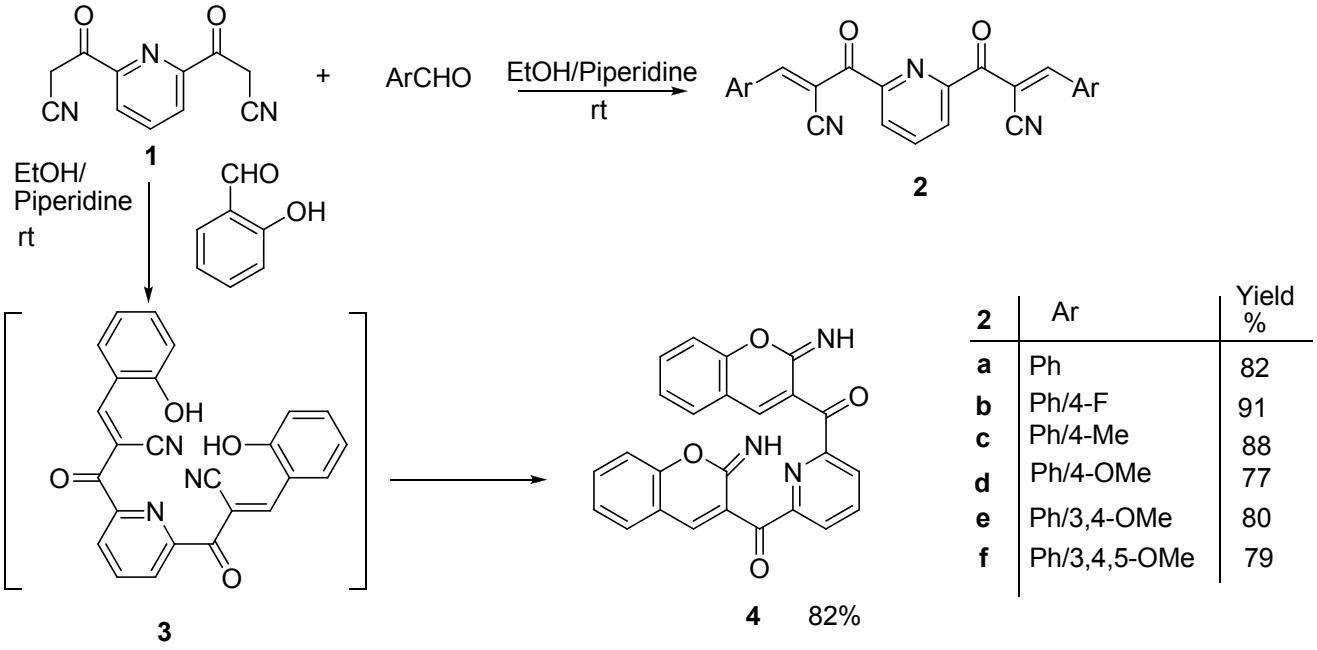
Binucleophiles are an important reagents in heterocyclic chemistry, and their reactions with electrophiles are a facile synthetic approach for obtaining divers heterocyclic systems containing azole and condensed azole moieties.[1-5] An interest on these heterocycles is attributed to their known biological activities.[6-12] Multicomponent condensation reactions (MCRs) consider as a powerful method for the synthesis of organic compounds, since the products are formed in a single step.[13,14] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure step.[15-18] In the last decade great deal of interest has been focused on the synthesis of the functionalized pyridine derivatives due to their biological activities.[19-22] In view of these observations and in continuation of our current interest in the synthesis of poly substituted heterocycles for biological evaluations,[23-30] we described herein a facile synthesis of novel 2.6-disubstituted pyridines with expected biological activity starting from pyridine-2,6-bis(2-benzylidene-3-oxopropanenitrile) (**2a**). Previously we have reported the synthesis of

2,6-bis[3-oxopropanenitrile-2(*N*,*N*-dimethylamino)methylene]pyridine and its reactivity towards some nitrogen binucleophiles.[31] As part of our current studies on the developments of different routes to heterocyclic systems bearing deferent type and number of substituents, we described herein a facile synthesis of pyridine-2,6-bis(2-benzylidene-3-oxopropanenitrile) (**2a**) and its reactivity towards some nitrogen binucleophiles to increase the number of substituent on the synthesized heterocycles and then study the effect of number of substituent in the biological activity. Herein we described also, a facile synthesis of fused pyridine derivatives (including pyrazolo[3,4-*b*]pyridine and pyrido[2,3-*d*]pyrimidine) by three-component one-pot reaction of benzaldehyde, pyridine-2,6-bis(3-oxopropanenitrile) (**1**), and electron-rich amino heterocycles in DMF under mild conditions.

RESULTS AND DISCUSSION

Substituted β-keto nitriles are highly reactive multifunctional synthetic intermediates which undergo a wide range of condensation and cyclization reactions.[32-36] Recently, we have reported the preparation of pyridine-2,6-bis(3-oxopropanenitrile) (**1**) *via* the Claisen condensation of diethyl 2,6-pyridinedicarboxylate with acetonitrile in dry THF, in the presence of sodium hydride as strong base.[30] The active methylene moiety of the β-keto nitrile **1** condensed with the appropriate aromatic aldehydes in EtOH and in the presence of a catalytic amount of piperidine to afford the corresponding Knoevenagel products: pyridine-2,6-bis-((*E*)-2-arylidene-3-oxopropanenitrile) (**2a-f**) (Scheme 1). The structure of the isolated Knoevenagel products (**2a-f**) were assigned as the *E*-isomer based on the previous reported paper.[37] The IR spectrum of compound **2a**, taken as a typical example of the series, exhibited a strong carbonyl and nitrile bands at 1721 and 2188 cm^{-1}, respectively. The ^1H NMR spectrum of **2a** revealed signal at δ 8.22 due to a methine proton, in addition to an multiplet at δ 6.77-8.01 due to phenyl and pyridine protons. On the other hand, treatment of pyridine-2,6-bis(3-oxopropanenitrile) (**1**) with salicylaldehyde afforded the coumarin derivative **4** based on the spectral data and similarity to the well-established behavior of 4-antipyrinyl acetonitrile on the reaction with salicylaldehyde to form 2-imino-2*H*-chromene derivatives.[38] The absence of cyano group signal at 2100-2200 cm^{-1} in the IR spectrum of compound **4** support its structure. The formation of compounds **4** could be explained by the reaction sequence as in Scheme 1. First a Knoevenagel condensation followed by intramolecular cyclization to coumarin derivative **4**.

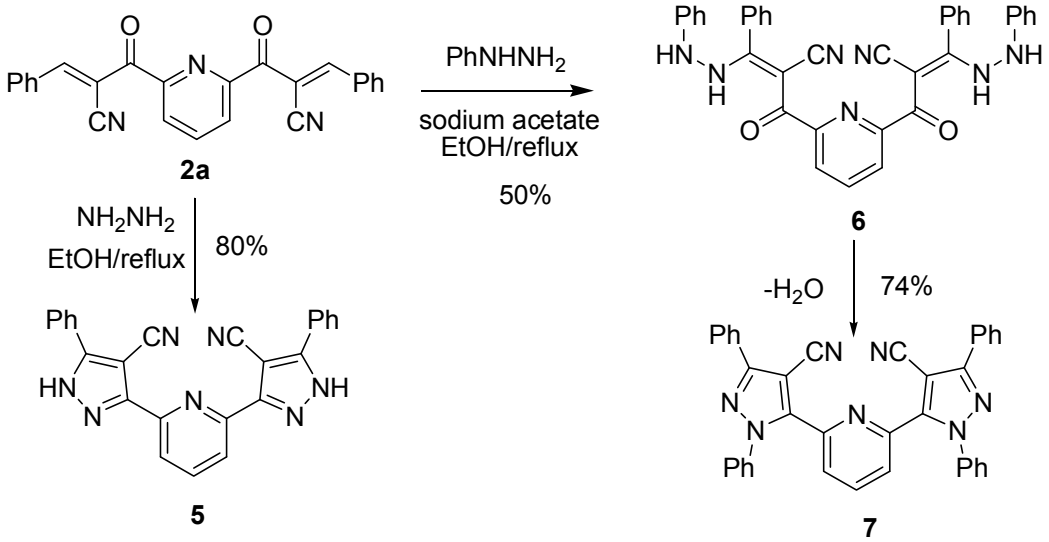
Subsequent addition of nitrogen-containing reagents that possess two nucleophilic centers provides a means to convert pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (**2a**) to functionalized heterocycles. Thus, treatment of 2-benzylidene-3-oxopropanenitrile **2a** taken as a typical example of the synthesized serieswith hydrazine hydrate, in refluxing EtOH, afforded the pyrazole derivative **5** as shown in Scheme 2.



2	Ar	Yield %
a	Ph	82
b	Ph/4-F	91
c	Ph/4-Me	88
d	Ph/4-OMe	77
e	Ph/3,4-OMe	80
f	Ph/3,4,5-OMe	79

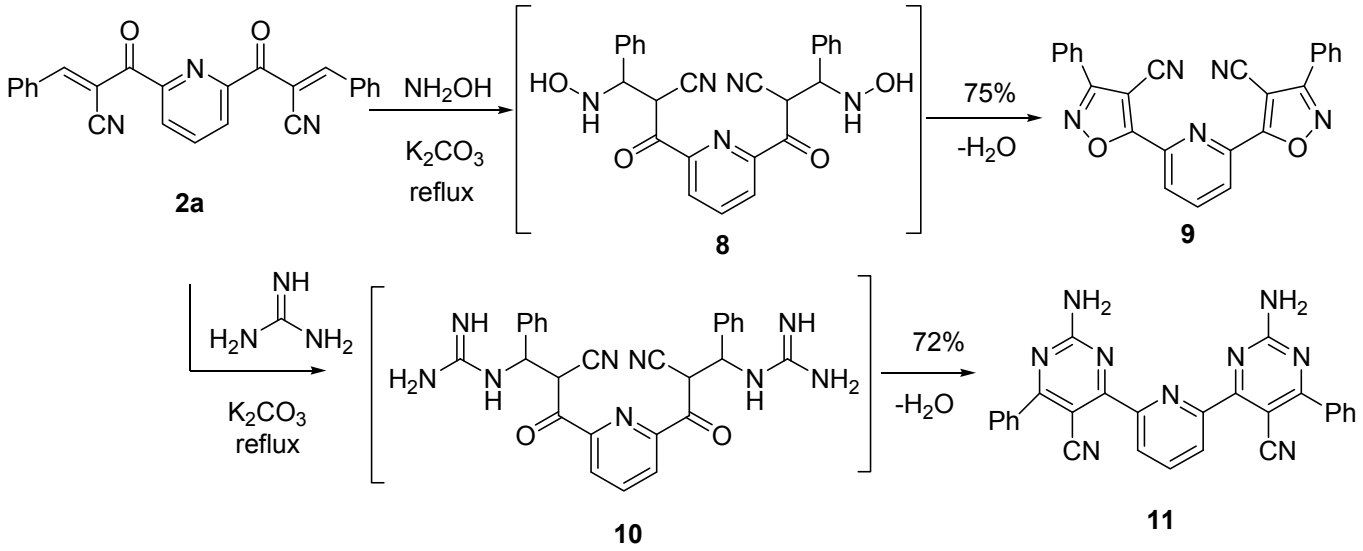
Scheme 1

The formation of compound **5** was assumed to proceed by a sequence of 1,4-addition, cyclization with loss of water, followed by late stage oxidation that is driven by the formation of an aromatic heterocycle. Pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (**2a**) reacts also with phenyl hydrazine in refluxing EtOH, in the presence of sodium acetate to afford the pyrazole derivative **7**. This reaction proceeds by initial 1,4-addition of phenyl hydrazine, followed by rapid oxidation to provide firstly stable vinylogous amide-like structure **6** due to the steric hindrance of phenyl group, then the vinylogous amide-like structure **6** converted to product **7** by loss of water (Scheme 2). The structures of the products **5**, **6** and **7** were confirmed on the bases of their elemental analysis and spectral data (See experimental part).



Scheme 2

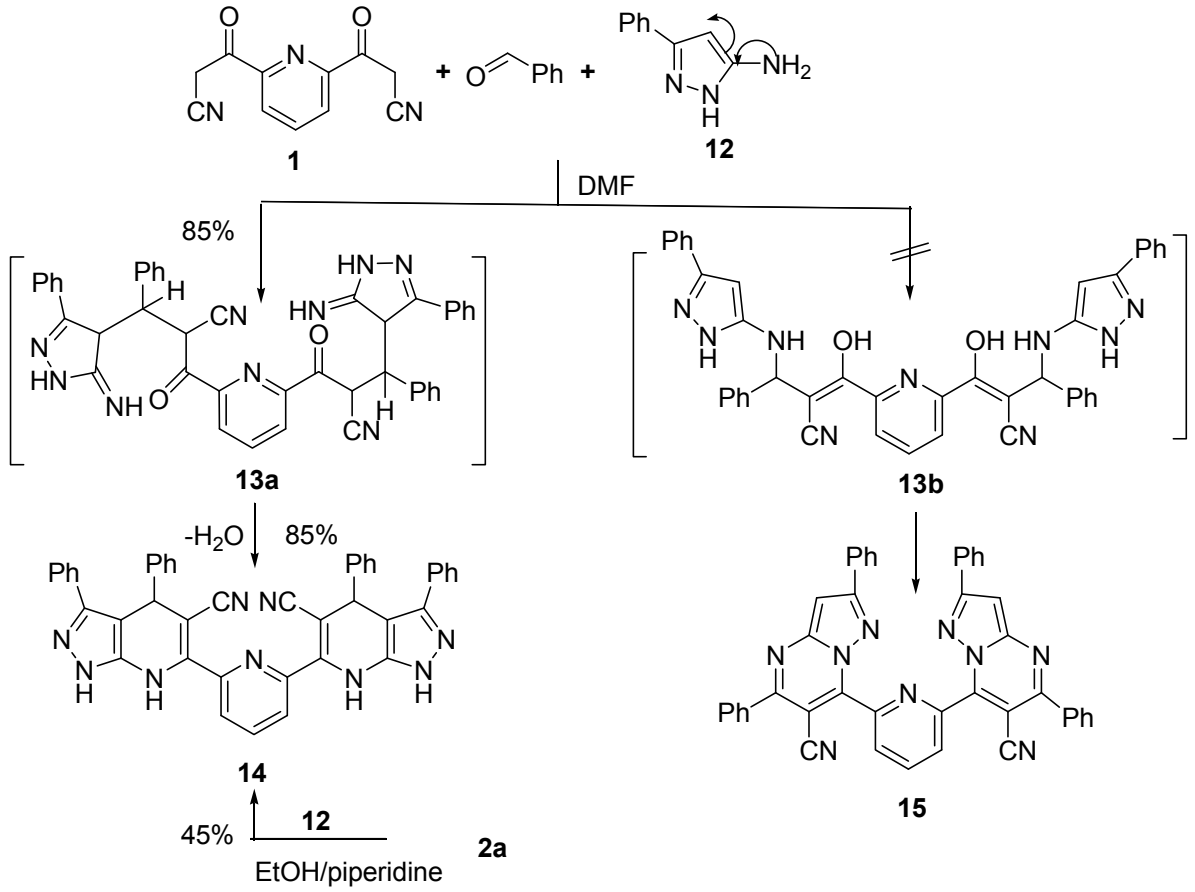
Compound **2a** reacts also with hydroxylamine hydrochloride, in the presence of sodium acetate, to afford white solid of 2,6-bis(4-cyano-3-phenylisoxazol-5-yl)pyridine (**9**) that is not readily soluble in DMSO, chloroform or methanol (therefore, it is difficult to measure its NMR spectra). Compound **9** is assumed to be formed *via* formation of non-isolable intermediate **8** which underwent condensation and intramolecular cyclization followed by oxidation that is driven by the formation of an aromatic heterocycle, to afford the isoxazole derivative **9** (Scheme 3). The IR spectrum of the later product revealed the lack of absorption band corresponding to carbonyl group and showed band at 2205 cm^{-1} corresponding to nitrile function and its mass spectrum revealed molecular ion peak at *m/z* 415. 2-Benzylidene-3-oxopropanenitrile **2a** reacts also with guanidine in refluxing EtOH, in the presence of anhydrous potassium carbonate to give a single productthat was identified as 2,6-bis(2-amino-5-cyano-6-phenylpyrimidin-4-yl)pyridine (**11**) according to its elemental analysis and spectral data (See experimental part) (Scheme 3).



Scheme 3

The behaviors of the benzylidene-3-oxopropanenitrile derivative **2a** towards electron-rich amino heterocycles were also investigated. Thus, treatment of compound **2a** with 5-amino-3-phenyl-1*H*-pyrazole (**12**), in refluxing EtOH in the presence of a catalytic amount of triethylamine, furnished a product identified as 2,6-bis[5-cyano-4,7-dihydro-3,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl]pyridine (**14**) (with 45% yield) and not **15** (Scheme 4) on the basis of its elemental analysis and spectral data. The ^{1}H NMR spectrum of **14** revealed two-D_2O-exchangeable signals at δ 10.37 and 12.38 due to NH protons of pyridine and pyrazole, respectivly. Furthermore, compound **14** was prepared with 85% yield by three-component one-pot reaction of aldehyde, 3-oxopropanenitrile **1**, and 5-amino-3-phenyl-1*H*-pyrazole (**12**), in DMF at room temperature. The formation of compounds **14** could be explained by the reaction sequence as in Scheme 4. First, a Knoevenagel condensation reaction of benzaldehydewith 3-oxopropanenitrile **1** is proposed to give (*E*)-2-benzylidene-3-phenyl-3-oxopropanenitrile (**2a**) followed

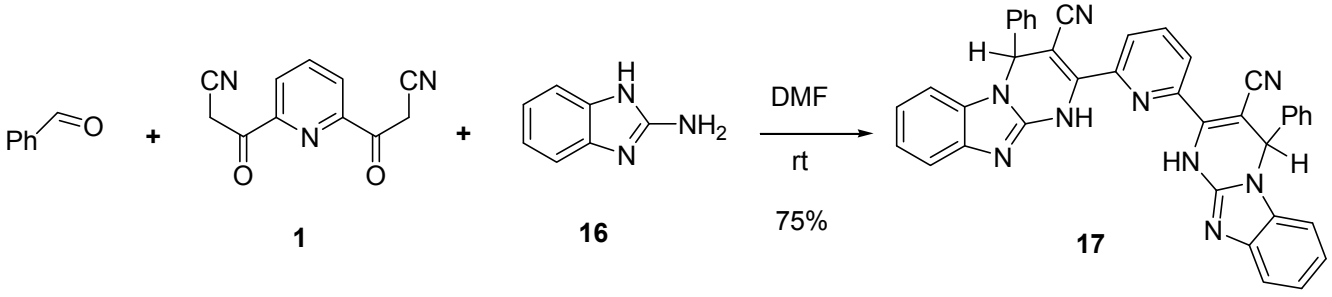
by Michael addition of electron-rich amino heterocyclic compound **12** to provide intermediate **13a**, that underwent condensation and intramolecular cyclization to afford compound **14** (Scheme 4).



Scheme 4

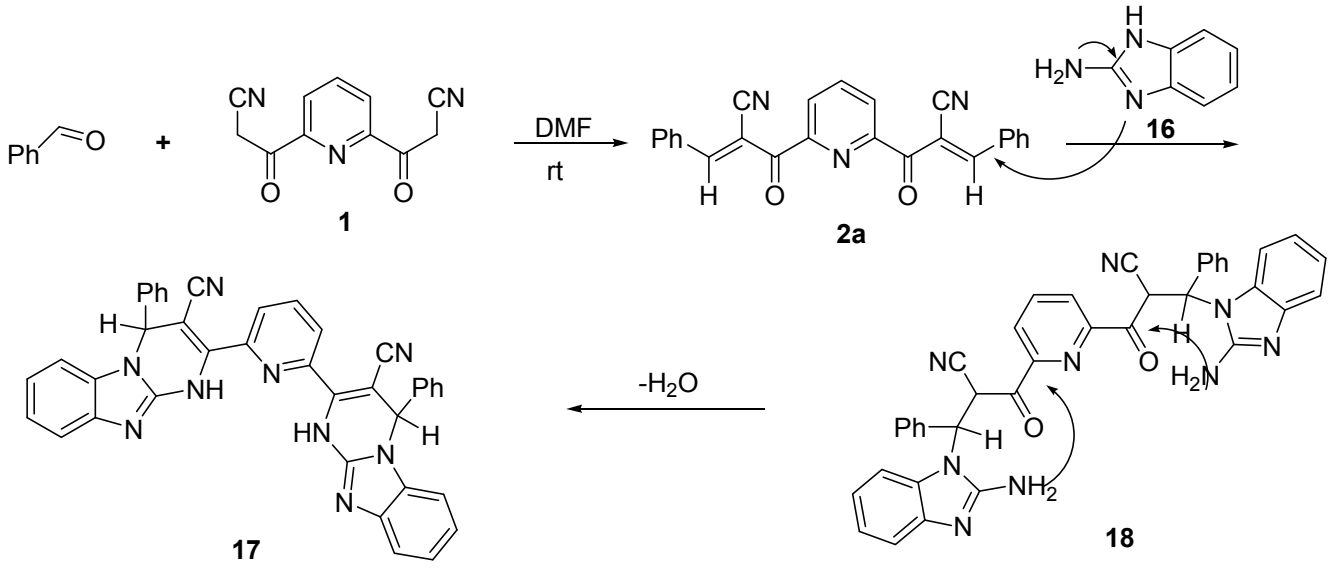
The yield of compound **14** from method B was lower compared to one pot synthesis of method A due to the solvent effect, DMF consider as aprotic solvent that enhance Michael addition of electron-rich amino heterocyclic compound **12** to provide intermediate **13a**.

Three-component one-pot condensation of an aldehyde, β-ketonitrile (**1**) instead of β-ketoester and 2-aminobenzimidazole, instead of thiourea in Biginelli and Biginelli like reactions,[39] in DMF at room temperature, afforded triheterocyclic dihydropyrimidine (DHPs) derivative (**17**) (Scheme 5).



Scheme 5

The latter reaction proceeds in two steps: first, Knoevenagel condensation of benzaldehyde with **1** followed by Michael addition of 2-aminobenzimidazole **16** followed by intramolecular cyclization to afford 4*H*-pyrimido[1,2-*a*]benzimidazole derivative **17** (Scheme 6).



Scheme 6

CONCLUSION

The present study describes syntheses of pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (**2a**) and its reactivity towards nitrogen binucleophiles such hydrazine, phenylhydrazine, hydroxylamine and guanidine to afford 2,6-bis(4-cyano-1*H*-3-phenylpyrazole-5-yl)pyridine (**5**), 2,6-bis(4-cyano-1*H*-1,3-diphenylpyrazole-5-yl)pyridine (**7**), 2,6-bis(4-cyano-3-phenylisoxazol-5-yl)pyridine (**9**) and 2,6-bis(2-amino-5-cyano-6-phenylpyrimidin-4-yl)pyridine (**11**). We have described also an efficient synthesis of one-pot three-component reaction of aldehyde, 3-oxoprobaoenitrile (**1**), and electron-rich amino heterocycles, such as 5-aminopyrazole or 2-aminobenzimedazole, in DMF for the synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine (**14**) and pyrimido[1,2-*a*]benzimidazole (**17**) derivative, respectively. This method has the advantages of higher yields, milder reaction conditions and shorter reaction time.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide discs on a PyeUnicam SP3-300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.46 MHz) were run in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the

Micro-analytical Centre of Cairo University, Giza, Egypt and recorded on Elementar-Vario EL (Germany) automatic analyzer. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F_{254}, Merck). Compounds **1**[30] and **12**[40-42] were prepared according to literature procedures.

Synthesis of pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) dreivatives (2a-f)

To a stirred solution of pyridine-2,6-bis(3-oxo-3-propanenitrile) (**1**) (0.21 g, 1 mmol) and the appropriate aldehyde (2 mmol) in EtOH (20 mL), few drops of piperidine were added. The resulting mixture was stirred for 2-4 h at rt and the solid that precipitate was collected by filtration, washed with EtOH, dried and finally recrystallized from EtOH to afford the corresponding 2-benzylidene-3-oxopropanenitrile dreivatives (**2a-f**).

Pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (2a)

Yield (0.32 g, 82%); brown solid (from EtOH); mp: 134-135 °C. IR (KBr, cm^{-1}): *v* 2188 (CN), 1721 (C=O). ^{1}H NMR (DMSO-d_6): δ 7.14-7.31 (m, 10H, Ar-H), 7.65-8.12 (m, 3H, pyridine-H), 8.22 (s, 2H, 2C=CH). ^{13}C NMR (DMSO-d_6): δ 116.46, 125.19, 125.40, 129.44, 139.44, 140.2, 148.43, 150.49, 151.14, 165.40, 190.45. MS *m/z* (%): 389 [M^+] (15), 232 (20), 128 (50), 77 (100). Anal. Calcd for $C_{25}H_{15}N_3O_2$ (389.41): C, 77.11; H, 3.88; N, 10.79. Found: C, 77.29; H, 3.97; N, 10.91.

Pyridine-2,6-bis-((*E*)-2-(4-fluorobenzylidene)-3-oxopropanenitrile) (2b)

Yield (0.39 g, 91%); orange crystals (from EtOH); mp: 263-265 °C. IR (KBr, cm^{-1}): *v* 2171 (CN), 1717 (C=O). ^{1}H NMR (DMSO-d_6): δ 7.01-7.33 (m, 8H, Ar-H), 7.51-8.01 (m, 3H, pyridine-H), 8.11 (s, 2H, 2C=CH). MS *m/z* (%): 425 [M^+] (53), 343 (15), 302 (33), 223 (48), 174 (63), 126 (90), 76 (100). Anal. Calcd for $C_{25}H_{13}F_2N_3O_2$ (425.39): C, 70.59; H, 3.08; N, 9.88. Found: C, 70.35; H, 3.18; N, 9.71.

Pyridine-2,6-bis-((*E*)-2-(4-methylbenzylidene)-3-oxopropanenitrile) (2c)

Yield (0.37 g, 88%); brown crystals (from EtOH); mp: 128-129 °C. IR (KBr, cm^{-1}): *v* 2203 (CN), 1717 (C=O). ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 6H, $2CH_3$), 6.75-7.34 (m, 8H, Ar-H), 7.71-8.10 (m, 3H, pyridine-H), 8.35 (s, 2H, 2C=CH). ^{13}C NMR (DMSO-d_6): δ 25.3, 116.4, 126.2, 126.3, 129.4, 139.1, 145.2, 149.3, 150.9, 152.2, 165.1, 188.5. Anal. Calcd for $C_{27}H_{19}N_3O_2$ (417.46): C, 77.68; H, 4.59; N, 10.01. Found: C, 77.61; H, 4.62; N, 10.11.

Pyridine-2,6-bis-((*E*)-2-(4-methoxybenzylidene)-3-oxopropanenitrile) (2d)

Yield (0.34 g, 77%); yellow crystals (from EtOH); mp: 138-139 °C. IR (KBr, cm^{-1}): *v* 2176 (CN), 1720 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.35 (s, 6H, $2OCH_3$), 6.82-7.23 (m, 8H, Ar-H), 7.77-8.10 (m, 3H, pyridine-H), 8.31 (s, 2H, 2C=CH). Anal. Calcd for $C_{27}H_{19}N_3O_4$ (449.46): C, 72.15; H, 4.26; N, 9.35. Found: C, 72.05; H, 4.46; N, 9.21.

Pyridine-2,6-bis-((*E*)-2-(3,4-dimethoxybenzylidene)-3-oxopropanenitrile) (2e)

Yield (0.41 g, 80%); yellow crystals (from EtOH); mp: 151-152 °C. IR (KBr, cm^{-1}): *v* 2181 (CN), 1720 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.65, 3.75 (s, 12H, $2OCH_3$), 6.81-7.31 (m, 4H, Ar-H), 7.65-8.11 (m, 3H,

pyridine-H), 8.17 (s, 2H, 2C=CH). MS *m/z* (%): 509 [M^+] (25), 77 (100). Anal. Calcd for $C_{29}H_{23}N_3O_6$ (509.51): C, 68.36; H, 4.55; N, 8.25. Found: C, 68.26; H, 4.61; N, 8.31.

Pyridine-2,6-bis-((*E*)-2-(3,4,5-trimethoxybenzylidene)-3-oxopropanenitrile) (2f)

Yield (0.45 g, 79%); pale yellow crystals (from EtOH); mp: 160-161 °C. IR (KBr, cm^{-1}): *v* 2182 (CN), 1714 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.60-3.85 (3s, 18H, 6 OCH_3), 6.59 (s, 4H, Ar-H), 7.77-8.15 (m, 3H, pyridine-H), 8.21 (s, 2H, 2C=CH). MS *m/z* (%): 569 [M^+] (5.4), 536 (2), 391 (16), 324 (4), 181 (27), 145 (47), 84 (100). Anal. Calcd for $C_{31}H_{27}N_3O_8$ (569.56): C, 65.37; H, 4.78; N, 7.38. Found: C, 65.31; H, 4.82; N, 7.35.

Pyridine-2,6-bis(1-imino-1*H*-isochromen-3-yl-methanone) (4)

Yield (0.33 g, 78%); pale yellow crystals (from EtOH); mp: 225-227 °C. IR (KBr, cm^{-1}): *v* 3415 (NH), 1720 (C=O). ^{1}H NMR (DMSO-d_6): δ 4.81 (s, 2H, 2NH, D_2O-exchangable), 6.70-8.05 (m, 8 Ar-H, 3 pyridine-H), 8.18 (s, 1H, CH). MS *m/z* (%): 421 [M^+] (10), 317 (30), 250 (35), 172 (72), 89 (60), 51 (100). Anal. Calcd for $C_{25}H_{15}N_3O_4$ (421.40): C, 71.25; H, 3.59; N, 9.97. Found: C, 71.05; H, 3.72; N, 9.72.

2,6-Bis(4-cyano-1*H*-3-phenylpyrazole-5-yl)pyridine (5)

Hydrazine hydrate (80%, 2 mL) was added to a stirred solution of compound **2a** (0.39 g, 1 mmol) in EtOH (10 mL). Stirring was continued for 4 h at rt and the obtained solid was filtered off, washed with cold water, dried and finally recrystallized from EtOHto affordcompound **5**. Yield (0.31 g, 75%); pale yellow powder (from EtOH); mp: 155-156 °C. IR (KBr, cm^{-1}): *v* 3273 (NH), 2191 (CN). ^{1}H NMR (DMSO-d_6): δ 6.71-8.13 (m, 13H, Ar-H and pyridine-H), 10.29 (br s, 2H, 2NH, D_2O-exchangeable). MS *m/z* (%): 413 [M^+] (15), 372 (25), 245 (55), 223 (45), 179 (75), 165 (67), 129 (93), 76 (100). Anal. Calcd for: $C_{25}H_{15}N_7$ (413.43): C, 72.63; H, 3.66; N, 23.72. Found: C, 72.77; H, 3.51; N, 23.87.

2,6-Bis(4-cyano-1*H*-1,3-diphenylpyrazole-5-yl)pyridine (7)

To a solution of the compound **2a** (0.39 g, 1 mmol) in EtOH (10 mL), were added phenyl hydrazine (0.32 g, 3 mmol) and sodium acetate (0.3 g). The reaction mixture was refluxed for 5 h, then left to cool and 10 mL of water was added. The yellowish solid precipitate was collected by filtration, washed with EtOH, dried, and finally recrystallized from EtOH to afforded 2,6-bis(4-cyano-1*H*-1,3-diphenylpyrazole-5-yl)pyridine) (**7**). Compound **6** was separated after 1 h.

Enehydrazine of pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (6)

Yield (0.31 g, 50%); pale yellow solid; mp: 147-148 °C. IR (KBr, cm^{-1}): *v* 3305 (2NH), 2258 (CN), 1707 (C=O). ^{1}H NMR (DMSO-d_6): δ 6.71-8.17 (m, 20H, Ar-H and 3H, pyridine), 7.82, 10.30 (s, 2H, 2NH-D_2O exchangable). MS *m/z* (%): 601 [M^+] (3), 503 (83), 371 (51), 186 (67), 128 (46), 91 (47), 77 (100). Anal. Calcd for $C_{37}H_{27}N_7O_2$ (601.66): C, 73.86; H, 4.52; N, 16.30. Found: C, 73.93; H, 4.32; N, 16.21.

2,6-Bis(4-cyano-1*H*-1,3-diphenylpyrazole-5-yl)pyridine (7)

Yield (0.42 g, 74%); pale yellow; mp: 165-166 °C. IR (KBr, cm^{-1}): *v* 2194 (CN). ^{1}H NMR (DMSO-d_6): δ

7.11-7.70 (m, 20H, Ar-H), 7.95-8.03 (m, 3H, pyridine). ^{13}C NMR (DMSO-d_6): δ 108.5, 115.3, 119.5, 120.4, 126.2, 126.3, 127.1, 129.5, 132.5, 135.1, 137.4, 139.2, 149.2, 150.9, 154.2, MS *m/z* (%): 569 [M^+] (54), 467 (36), 141 (11), 141 (47), 92 (76), 76 (100). Anal. Calcd for $C_{37}H_{27}N_7$ (569.66): C, 78.01; H, 4.88; N, 17.21. Found: C, 78.11; H, 4.70; N, 17.31.

Reaction of pyridine-2,6-bis-((*E*)-2-benzylidene-3-oxopropanenitrile) (2a) with hydroxylamine hydrochloride and guanidine.

To a mixture of compound **2a** (0.39 g, 1 mmol) and hydroxylamine hydrochloride (0.14 g, 2 mmol) or guanidine hydrochloride (0.19 g, 2 mmol) in EtOH (20 mL), was added anhydrous potassium carbonate (0.28 g, 2 mmol). The resulting mixture was refluxed for 6-10 h, and allowed to cool to rt then diluted with water (30 mL). The solid products that formed were collected by filtration, washed with water, dried and finally recrystallized from the proper solvent to afford compounds **9** and **11** respectively.

2,6-Bis(4-cyano-3-phenylisoxazol-5-yl)pyridine (9)

Yield (0.31 g, 75%); white solid (DMF); mp: 230-232 °C. IR (KBr, cm^{-1}): *v* 2205 (CN). MS *m/z* (%): 416 (M^++1) (5), 415 [M^+] (10), 272 (13), 234 (41), 206 (21), 190 (16) 122 (63), 105 (54), 77 (74), 51 (100). Anal. Calcd for $C_{25}H_{13}N_5O_2$ (415.4): C, 72.28; H, 3.15; N, 16.86. Found: C, 72.38; H, 3.25; N, 16.71.

2,6-Bis(2-amino-5-cyano-6-phenylpyrimidin-4-yl)pyridine (11)

Yield (0.34 g, 72%); brown solid (from DMF); mp:>300 °C. IR (KBr, cm^{-1}): *v* 3392-3100 (NH_2), 2200 (CN). ^{1}H NMR (DMSO-d_6): δ 4.33 (br s, 4H, 2NH_2, D_2O-exchangeable), 7.11-8.08 (m, 13H, Ar-H and pyridine-H), ^{13}C NMR (DMSO-d_6): δ 95.1, 115.2, 120.1, 125.4, 127.3, 129.5, 130.1, 135.7, 150.1, 167.5, 169.8, 171.1. MS *m/z* (%): 467 [M^+] (5), 430 (10), 360 (11), 319 (7), 272 (36) 233 (29), 173 (16), 128 (41), 105 (66), 77 (100). Anal. Calcd for $C_{27}H_{17}N_9$ (467.48): C, 69.37; H, 3.67; N, 26.97. Found: C, 69.23; H, 3.52; N, 26.81.

Three component one pot synthesis of fused pyridine and pyrimidine derivatives 14 and 17

General Procedure: Method A: a mixture of benzaldehyde (0.22 g, 2 mmol), 3-oxopropanenitrile **1** (0.21 g, 1 mmol) and the appropriate heterocyclic amine **12** or **16** (1 mmol) in dry DMF (10 mL) was stirred at rt for 4-7 h to complete the reaction (monitored by TLC), then 50 mL water was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from EtOH to give **14** and **17**, respectively. Method B: To a mixture of the 2-benzylidene-3-oxopropanenitrile (**2**) (0.39 g, 1 mmol) and 5-amino-3-phenyl-1*H*-pyrazole **13** (0.32 g, 2 mmol) in EtOH (20 mL), was added a few drops of piperidine. The resulting mixture was refluxed for 5 h, and allowed to cool to rt. The solid product that formed was collected by filtration, washed with EtOH, dried and finally recrystallized from EtOH to afford 2,6-bis[6-cyano-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-yl]pyridine **14**.

2,6-Bis[5-cyano-4,7-dihydro-3,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl]pyridine (14)

Yield [method A (0.57 g, 85%), method B (0.30 g, 45%)]; pale yellow crystals (from MeOH); mp:

265-267 °C. IR (KBr, cm^{-1}): *v* 3328, 3242 (2NH), 2191 (CN). ^{1}H NMR (DMSO-d_6): δ 5.69 (s, 2H, 2CH), 7.23-7.49 (m, 20H, Ar-H), 7.51-8.02 (m, 3H, pyridine-H), 10.37, 12.38 (s, 2H, 2NH-D_2O-exchangable). ^{13}C NMR (DMSO-d_6): δ 29.11, 81.47, 100.14, 111.52, 119.13, 124.13, 126.85, 127.38, 128.01, 128.45, 128.62, 134.11, 135.17, 139.13, 145.76, 148.13, 151.06, 161.07. MS *m/z* (%): 671 [M^+] (15), 669 (15) 579 (20), 343 (4), 127 (12), 104 (53), 90 (67), 76 (100). Anal. Calcd for $C_{43}H_{29}N_9$ (671.75): C, 76.88; H, 4.35; N, 18.77. Found: C, 76.93; H, 4.27; N, 18.81.

2,6-Bis[4-phenyl-3-cyano-1,4-dihydropyrimido[1.2-*a*]benzimidazol-2-yl]pyridine (17)

Yield (0.49 g, 75%, pale yellow crystals); mp: 244-246 °C. IR (KBr, cm^{-1}): *v* 3433 (NH) 2187 (CN). ^{1}H NMR (DMSO-d_6): δ 4.59 (d, 2H, 2CH), 6.54-7.10 (m, 18H, Ar-H), 7.97-8.13 (m, 3H, pyridine-H), 8.33 (s, 2H, 2NH-D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 47.12, 95.11, 112.1, 118.12, 118.5, 119.7, 119.9, 120.11, 122.11, 127.12, 128.30, 128.6, 133.21, 135.12, 140.11, 142.5, 159.11, 161.41, 165.14. Anal. Calcd for $C_{39}H_{25}N_9$ (619.68): C, 75.59; H, 4.07; N, 20.34. Found: C, 75.35; H, 4.19; N, 20.23.

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