

A new convenient synthesis of some novel 2,6-disubstituted-pyridine derivatives

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Abstract

The versatile, hitherto unreported pyridine-2,6-bis-(3-oxo-3-propanenitrile) **2** was prepared by the Claisen condensation of pyridine-2,6-dicarboxylic acid ester **1** with acetonitrile in the presence of sodium hydride. Several new pyrazoles, isoxazoles, and pyrazolopyridazine derivatives have been synthesized by the reaction of pyridine-2,6-bis-(3-oxo-3-propanenitrile) **2** with bidentate nucleophilic reagents and hydrazonoyl chloride derivatives.

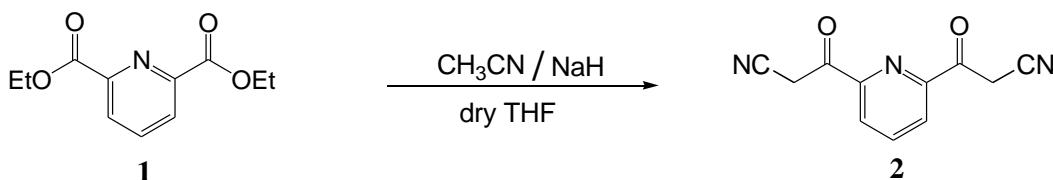
Keywords: Pyridine-2,6-bis-(3-oxo-3-propanenitrile), pyrazole, isoxazole, and hydrazonoyl chloride, pyrazolopyridazine

Introduction

Substituted 3-oxopropanenitriles represent a category of versatile synthetic intermediates. They provide miscellaneous building blocks in the synthesis of several types of heterocyclic ring systems based on a wide range of condensation and cyclization reactions.¹⁻⁹ On the other hand, a great deal of interest has been focused on the synthesis of the functionalized pyridine derivatives due to their biological activities.^{10,11} For example, some 2-pyridine radicals are incorporated into the structures of cardiotoxic agents such as milrinone¹² and HIV-1 specific transcriptase inhibitors.¹³ Furthermore, pyrazoles have also important applications in medicinal chemistry. For example, they have emerged as analgesic and anti-inflammatory drugs.^{14,15} In view of these observations and in continuation of our work on the synthesis of heterocyclic systems for biological evaluations,¹⁶⁻¹⁹ we considered it attractive to synthesize some pyrazoles and isoxazoles incorporated into pyridine moiety at position 2 and 6. Hitherto unrecorded pyridine-2,6-bis-(3-oxo-3-propanenitrile) **2** was prepared, and used as a building block for the synthesis of the title compounds.

Results and Discussion

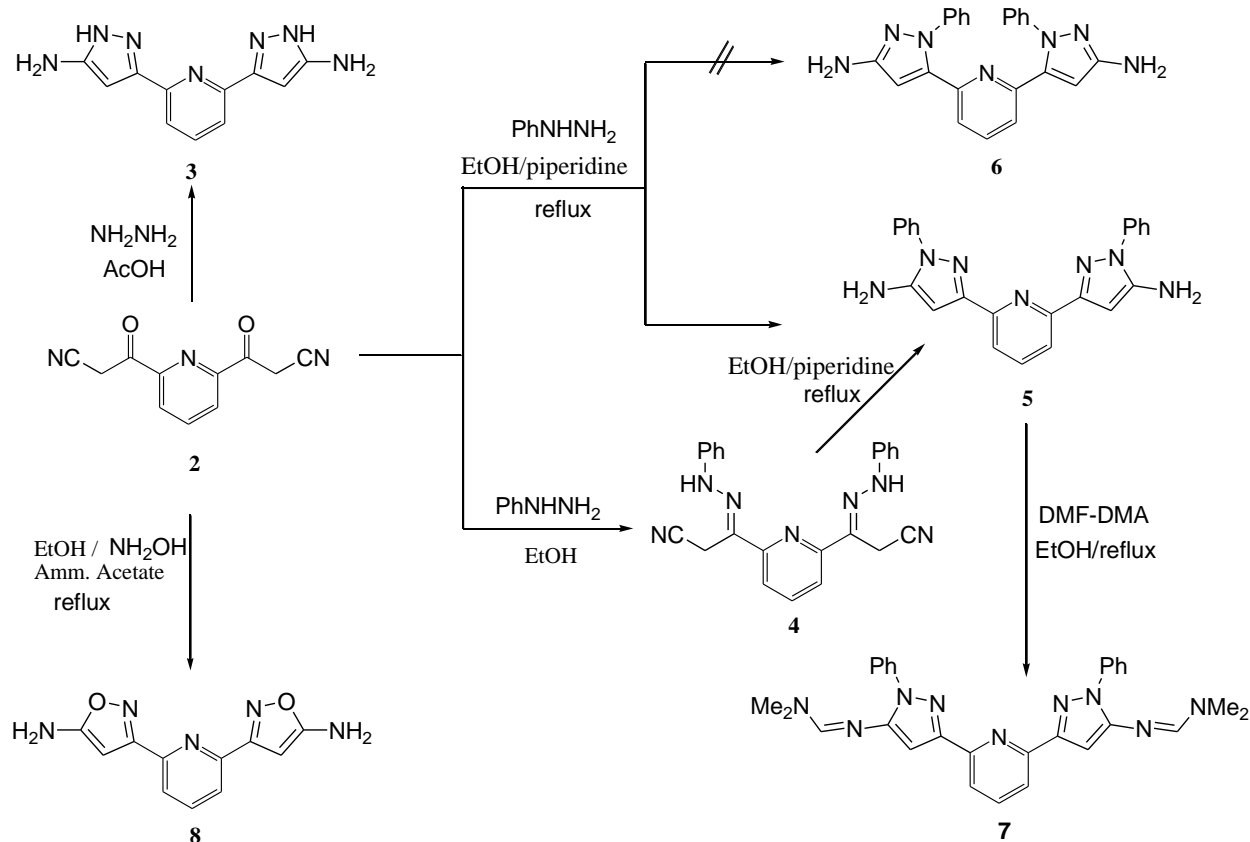
3-Oxoalkanonitriles can be generally prepared *via*: (i) acylation of active nitriles in the presence of suitable basic catalysts;²⁰⁻²² (ii) reacting α -halo ketones with cyanide ion,²³ and (iii) hydrolysis of β -enaminonitriles⁷. We decided to develop our synthesis of compound **2** *via* the Claisen condensation of 2,6-pyridine dicarboxylic ethyl ester **1** with acetonitrile in dry THF in the presence of sodium hydride as strong base (Scheme 1).



Scheme 1

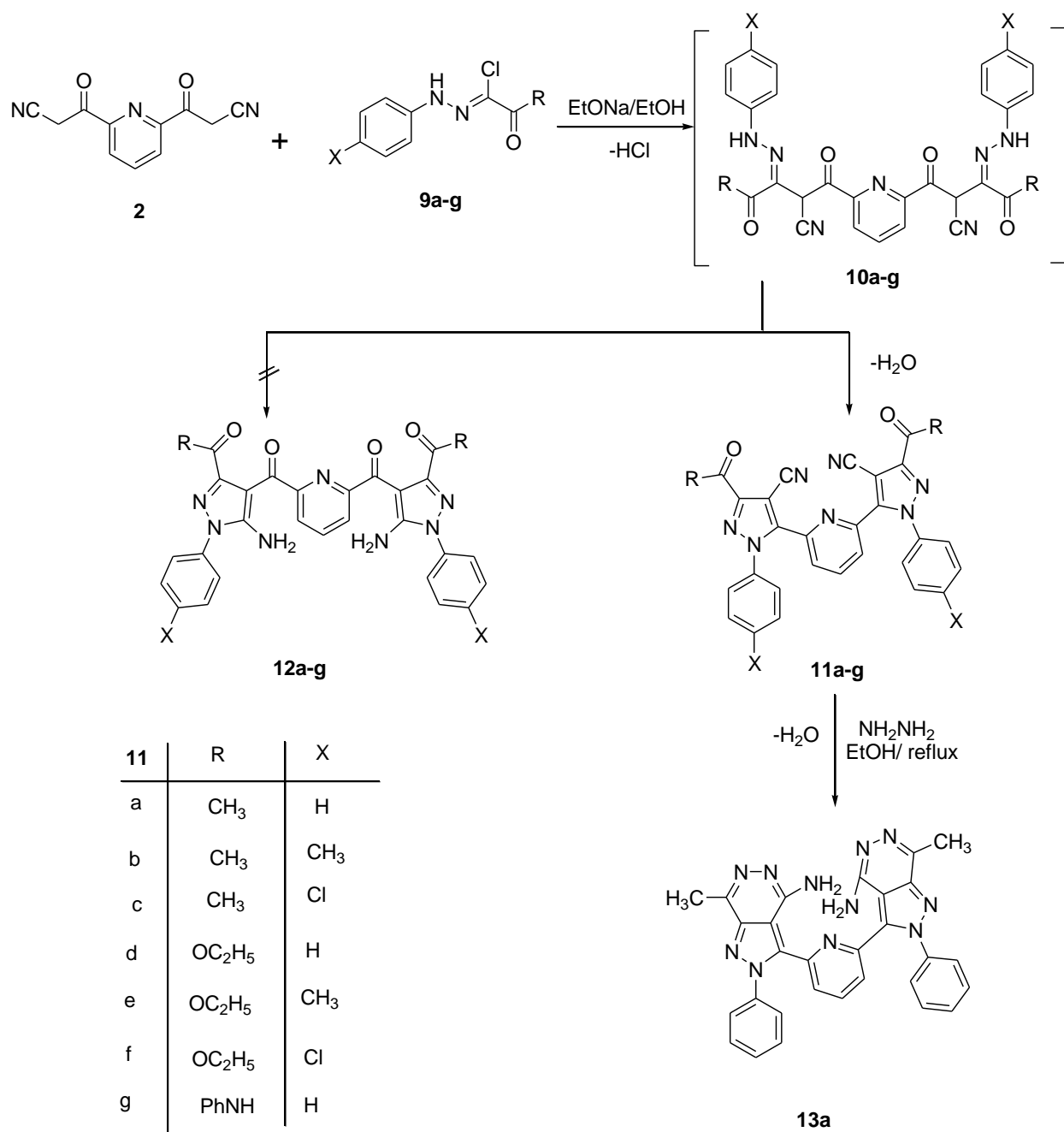
The unique reactivity of oxonitriles arises from the closeness of two strongly electron withdrawing groups. In general, the reactions of saturated oxonitriles reflect the high acidity of protons adjacent to carbonyl and nitrile group. Moreover, the keto and cyano functions are suitably situated to facilitate reactions with common bidentate reagents.²⁴

Treatment of pyridine-2,6-bis(3-oxo-3-propanenitrile) **2** with hydrazine hydrate in acetic acid, at room temperature, afforded a single product identified as 2,6-bis(5-amino-1*H*-pyrazol-3-yl)pyridine **3**. Compound **2** reacted with phenyl hydrazine in ethanol in the presence of a catalytic amount of piperidine, to yield a product which may be formulated as **5** or its isomer **6** (Scheme 2). The formation of compound **5** is assumed to proceed *via* condensation of the unsubstituted nitrogen atom of phenyl hydrazine with the carbonyl function in the oxonitriles **2** followed by intramolecular cyclization. Structure **5** was considered for a product based on similarity to the well established behavior of acyl and aroyl acetonitrile on the reaction with aryl hydrazines.²⁵ Structure **5** was further confirmed by the treatment of oxonitriles **2** with phenyl hydrazine at room temperature to give the open structure **4** which undergoes intramolecular cyclization when refluxed in ethanol in the presence of piperidine to afford a compound identical in all respects (TLC, mp, and spectra) with those of compound **5** (Scheme 2). Treatment of compound **5** with dimethylformamide-dimethylacetal (DMF-DMA) under reflux, afforded 2,6-bis-*N,N*-dimethyl-*N'*-(1-phenyl-1*H*-pyrazol-5-yl)formamide-3-yl]pyridine **7** (Scheme 2). The ¹H NMR spectrum of the later compound revealed two singlets at δ 2.98 and 3.11 due to methyl protons in addition to a singlet signals at δ 6.75 and 7.90 due to methylenes and pyrazole protons, respectively. In addition to a multiplet at δ 7.32-7.65 and δ 7.95-8.02 due to aromatic and pyridine protons, respectively. Compound **2** reacted similarly with hydroxylamine to afford the corresponding 5-aminoisoxazole derivative **8** (Scheme 2). It should be noted here that, the reaction of 3-oxoalkanonitrile with hydroxylamine hydrochloride has been reported by Elnagdi *et al.*²⁶ to yield amidoximes, that cyclized into 3-aminoisoxazoles.



Scheme 2

The reactivity of compound **2** towards a variety of hydrazoneyl chlorides was also examined. Thus, treatment of compound **2** with (*C*-acetyl-, *C*-ethoxycarbonyl, or *C*-acetanilido-)-*N*-arylhydrazoneyl chlorides **9a-g** and sodium ethoxide, in absolute ethanol furnished, in each case, only one isolable product. The identities of the isolated products were assigned as the pyrazole derivatives **11a-g** on the basis of their elemental analysis and spectral data (Scheme 3). For example, the IR spectra of compounds **11a-g** showed, in each case, the presence of nitrile and carbonyl stretching bands near 2200 and 1700 cm^{-1} respectively, and revealed the lack of a band characteristic for amino group [see Exp. Part]. The ^1H NMR spectrum of **11c** taken as an example of the series synthesized, displayed signal at δ 2.40 due to two acetyl groups, aromatic multiplet in the region δ 7.30-7.48, in addition to a multiplet at δ 7.95-8.03 due to pyridine protons and revealed the lack of a band characteristic for amino group. The possibilities of formation of the products **12a-g** are excluded on the basis of the spectral data and the chemical behavior of the reaction products with hydrazine hydrate. The corresponding pyrazolopyridazine derivative **13a** was obtained by the reaction of acetyl pyrazole **11a** with an excess of hydrazine upon refluxing in ethanol for 5h. The lack of nitrile functions in the IR spectra of the isolated products supported the formation of structure **13a** (Scheme 3).



Scheme 3

Experimental Section

General. All melting points were measured on Electro thermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. The NMR Spectra were

recorded at 270 MHz on a Varian Mercury VX-300 NMR spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75.46 MHz) were run in deuterated chloroform (CDCl_3) or dimethylsulphoxide ($\text{DMSO}-d_6$). 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 Microanalytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F₂₅₄, Merck). Hydrazonoyl chlorides **9a-g**²⁷⁻²⁹ were prepared as reported in the literature.

Pyridine-2,6-bis-(3-oxo-3-propanenitrile) (2). To a mixture of 2,6-pyridine dicarboxylic ethyl ester (**1**) (4.46 g, 20 mmol) and acetonitrile (2.70 mL, 50 mmol), in dry THF (50 mL), was added sodium hydride (4 g, 50 %). The reaction mixture was refluxed for 2h, and then allowed to cool. The solid that precipitated was filtered off, washed with diethyl ether and dried. The crude product was dissolved in water (30 mL) and the resulting alkaline solution was treated with concentrated hydrochloric acid until it becomes slightly acidic (pH 5). The precipitated solid product was filtered off, washed with water, dried and finally recrystallized to afford pyridine-2,6-bis-(3-oxo-3-propanenitrile) (**2**). Yield 80 %; brown crystals (from ethanol/dioxan); mp 185-186 °C. IR (KBr): ν 2264 (CN), 1720 (C=O) cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 3.74 (s, 2H, CH_2), 8.57-8.24 (m, 3H, pyridine). ^{13}C NMR ($\text{DMSO}-d_6$): δ 29.6, 116.4, 123.7, 126.4, 165.7, 190.7; MS m/z (%): 213 [M^+] (75), 145 (100). Anal. Calcd for $\text{C}_{11}\text{H}_7\text{N}_3\text{O}_2$ (213.19): C, 61.97 ; H, 3.31 ; N, 19.71. Found: C, 61.94 ; H, 3.34; N, 19.75.

2,6-Bis(5-amino-1H-pyrazol-3-yl)pyridine (3). Hydrazine hydrate (80 %, 2 mL) was added to a stirred solution of compound **2** (0.21 g, 1 mmol) dissolved in acetic acid (10 mL). Stirring was continued for 7 h at room temperature and the obtained solid was filtered off, washed with cold water, dried and finally recrystallized to afford compound **3**. Yield 75 %; white crystals (from ethanol/DMF); mp 261-262 °C. IR (KBr): ν 3302, 3275, 3200 (NH), (NH₂) cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 4.01 (br s, 4H, D₂O-exchangeable, 2NH₂), 6.09 (s, 2H, pyrazole), 7.50-7.81 (m, 3H, pyridine), 10.95 (s, 1H, D₂O-exchangeable, NH). MS m/z (%): 241 [M^+] (100), 212 (10), 185 (25), 76 (13). Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_7$ (241.11): C, 54.76; H, 4.60; N, 40.64. Found: C, 54.81 ; H, 4.65; N, 40.61.

E,E-2,6-Bis[3-(2-phenylhydrazino)-3-propanenitrile]pyridine (4). A mixture of compound **2** (0.21g, 1 mmol), phenylhydrazine (0.30 g, 3 mmol), in ethanol (10 mL), was stirred at room temperature for 3h. The formed solid was filtered off, dried and recrystallized to afford compound **6**. Yield 85%; white powder (from ethanol); mp 217-218 °C. IR (KBr): ν 3319 (NH), 2240 (CN) cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 4.34 (s, 4H, 2CH₂), 7.15-7.34 (m, 10H, ArH's), 7.67-8.03 (m, 3H, pyridine), 10.27 (s, 1H, D₂O-exchangeable, NH). MS m/z (%): 393 [M^+] (100). Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_7$ (393.44): C, 70.21; H, 4.87; N, 24.92. Found: C, 70.25; H, 4.84; N, 24.89.

2,6-Bis[5-amino-1-phenyl-1H-pyrazol-3-yl]pyridine(5)

Method A. To a solution of **2** (0.21 g, 1 mmol), in ethanol (10 mL), were added phenylhydrazine (0.30 g, 3 mmol) and few drops of piperidine. The reaction mixture was refluxed for 5h then

allowed to cool. The formed solid was filtered off, dried and recrystallized to afford compound **5** (yield 90%)

Method B. To a solution of **4** (0.21 g, 0.05 mmol), in ethanol (10 mL), were added few drops of piperidine. The reaction mixture was refluxed for 3h then allowed to cool. The formed solid was filtered off, dried and recrystallized afford a product identical in all respects (mp, mixed mp, TLC, IR and mass spectra with that obtained via method A (yield 95%). Yellow needles (from ethanol/dioxan); mp 241-242 °C. IR (KBr): ν 3321, 3216 (NH₂) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 5.48 (s, 4H, D₂O-exchangeable 2NH₂), 6.19 (s, 2H, pyrazole), 7.53 -7.67 (m, 10H, ArH's), 7.85-8.01 (m, 3H, pyridine). ¹³C NMR (DMSO-*d*₆): δ 89.1, 118.3, 123.7, 127.2, 129.8, 137.4, 139.7, 148.7, 151.6, 152.2; MS *m/z* (%):393 [M⁺] (100), 77 (90.6). Anal. Calcd for C₂₃H₁₉N₇ (393.44): C, 70.21; H, 4.87; N, 24.92. Found: C, 70.15; H, 4.87; N, 24.95.

2,6-Bis[*N,N*-dimethyl-*N'*-(1-phenyl-1*H*-pyrazol-5-yl)formamide-3-yl]pyridine (7). A solution of compound **5** (0.39 g, 1 mmol) and dimethylformamide-dimethylacetal (DMF-DMA) (0.24 g, 2 mmol), in absolute ethanol (10 mL), was refluxed for 4h, and then allowed to cool. The solid product was filtered off, washed with ethanol, dried and crystallized to afford compound **7**. Yield 85 %; Yellow needles (from ethanol/dioxan); mp 202-203 °C. IR (KBr): ν 1634 (C=N) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.98, 3.11 (2s, 12H, 4CH₃), 6.75 (s, 2H, pyrazole-H-4), 7.30-7.48(m, 10H, ArH's), 7.90 (s, 2H, CH enamine), 7.95-8.03 (m, 3H, pyridine). ¹³C NMR (DMSO-*d*₆): δ 34.5, 40.1,90.1, 118.5, 123.6, 125.8, 128.3, 128.4, 136.7, 140.4, 151.7, 152.4, 152.8, 154.8; MS *m/z* (%):503 [M⁺] (100), 371 (15),186 (69),77(63). Anal. Calcd for C₂₉H₂₉N₉ (503.60): C, 69.16; H, 5.80; N, 25.03. Found: C, 69.12; H, 5.84; N, 25.06

2,6-Bis(5-aminoisoxazol-3-yl)pyridine (8). To a solution of **2** (0.42 g, 2 mmol), in ethanol (10 mL), were added hydroxylamine hydrochloride (0.28 g, 4 mmol) and ammonium acetate (0.6 g). The reaction mixture was refluxed for 4h, and then poured onto ice cold water. The resulting solid was filtered off, washed with cold water, dried and recrystallized to afford 2,6-Bis[5-aminoisoxazol-3-yl]pyridine **8**. Yield 75 %; brown solid (from ethanol/dioxan); mp 232-234 °C. IR (KBr): ν 3310, 3193 (NH₂) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 5.52 (s, 4H, D₂O-exchangeable, 2NH₂), 6.85 (s, 2H, isoxazole-H-4), 7.90-8.05 (m, 3H, pyridine). ¹³C NMR (DMSO-*d*₆): δ 76.5, 121.7, 138.6, 149.4, 163.8, 171.8; MS *m/z* (%):243 [M⁺] (100), 243 (70), 226 (163), 160 (202), 144 (13), 117 (20.1), 90 (60), 54 (100). Anal. Calcd for C₁₁H₉N₅O₂ (243.22): C, 54.32; H, 3.73; N, 28.79. Found: C, 54.36; H, 3.70; N, 28.74.

Reaction of 2,6-Bis(3-oxo-3-propanenitrile) pyridine(2) with the hydrazonoyl halide derivatives. General procedure

3-Oxopropanenitriles **2** (0.42 g, 2 mmol) was added to a stirred ethanolic sodium ethoxide solution [prepared from sodium metal (0.11 g) and absolute ethanol (20 mL)]. After stirring for 20 min, the appropriate hydrazonoyl halide **9a-g** (4 mmol) was added and the reaction mixture was stirred at room temperature for 14 h. The formed solid was collected by filtration, washed with water, dried and finally recrystallized from the appropriate solvent, to afford the corresponding pyrazole pyridine derivatives **11a-g**.

2,6-Bis[3-acetyl-4-cyano-1-phenyl-1H-pyazol-5-yl]pyridine (11a). Yield 80%; yellow micro crystals (from ethanol-dioxan); mp > 300 °C. IR (KBr): ν 1671(C=O), 2210 (CN) cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.5(s,6H,2CH₃-acetyl)7.34 (m, 10H, ArH's), 8.03(m, 3H, pyridine). MS m/z (%):497 (M⁺) (30), 496 (10), 395 (30), 298 (51), 191 (54), 93 (100), 77 (25). Anal. Calcd for C₂₉H₁₉N₇O₂ (497.51): C, 70.01; H, 3.85; N, 19.71. Found C, 70.04; H, 3.81; N, 19.74

2,6-Bis[3-acetyl-4-cyano-1-1H-pyazol-*p*-tolyl 5-yl]pyridine (11b). Yield 83%; green solid (from ethanol/dioxan); mp > 300 °C. IR (KBr): ν 2198 (CN), 1655 (C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.10, (s, 6H, 2CH₃-tolyl), 2.45 (s, 6H, 2CH₃-acetyl), 7.34 (m, 10H, ArH's), 8.03 (m, 3H, pyridine). MS m/z (%): 525 [M⁺] (30), 524 (14), 313 (10), 174 (17), 121 (28), 92 (20), 57 (100). Anal. Calcd for C₃₁H₂₃N₇O₂ (525.56): C, 70.84; H, 4.41; N, 18.66. Found: C, 70.80; H, 4.38; N, 18.62.

2,6-Bis[3-acetyl-1-(4-chlorophenyl)-4-cyano-1H-pyazol-5-yl]pyridine (11c). Yield 85%; yellow solid (Ethanol); mp 238-240 °C. IR (KBr): ν 2237 (CN), 1678 (C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 2.40 (s, 6H, 2CH₃-acetyl), 7.32-7.65 (m, 8H, ArH's), 7.95-8.02 (m, 3H, pyridine). MS m/z (%): 565 (M⁺) (35), 540 (61), 499 (33), 414 (16), 346 (68), 239 (45), 152 (78), 111 (100). Anal. Calcd for C₂₉H₁₇Cl₂N₇O₂ (566.08): C, 61.50; H, 3.03; N, 17.31. Found: C, 61.54; H, 3.06; N, 17.34.

2,6-Bis[4-cyano-3-ethoxycarbonyl-1-phenyl-1H-pyrazol-5-yl]pyridine (11d). Yield 75%; Yellow needles (from ethanol); mp 234-235 °C. IR (KBr): ν 2184 (CN), 1725 (C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.32 (t, 6H, 2CH₃), 4.39 (q, 4H, 2CH₂), 7.34-7.56 (m, 10H, ArH's), 7.90-8.03 (m, 3H, pyridine). MS m/z (%):557 (M⁺) (35), 556 (49), 510 (28), 242 (16), 206 (17), 77 (100). Anal. Calcd for C₃₁H₂₃N₇O₄ (557.56): C, 66.78; H, 4.16; N, 17.59. Found: C, 66.74; H, 4.19; N, 17.63.

2,6-Bis[4-cyano-3-ethoxycarbonyl-1H-pyrazol-1-tolyl-5-yl]pyridine (11e). Yield 78 %; Yellow micro crystals (from ethanol/dioxan); mp > 300 °C. IR (KBr): ν 2263 (CN), 1721 (C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.35 (t, 6H, 2CH₃), 2.09 (s, 6H, 2CH₃-tolyl), 4.4 (q, 4H, 2CH₂), 7.25-7.46 (m, 8H, ArH's), 7.69-8.10 (m, 3H, pyridine). MS m/z (%): 585 (M⁺) (38). Anal. Calcd for C₃₃H₂₇N₇O₄ (585.61): C, 67.68; H, 4.65; N, 16.74. Found: C, 67.65; H, 4.61; N, 16.70.

2,6-Bis[1-(4-chlorophenyl)-4-cyano-3-ethoxycarbonyl-1H-pyrazol-5-yl]pyridine (11f)
Yield 80%; Yellow solid (from ethanol/dioxan); mp > 300 °C. IR (KBr): ν 2162 (CN), 1742 (C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 1.37 (t, 6H, 2CH₃), 4.12(q, 4H, 2CH₂), 7.34-7.41 (m, 10H, ArH's), 7.65-7.95 (m, 3H, pyridine). ^{13}C NMR (DMSO- d_6): δ 13.7, 63.2, 117.3, 120.0, 121.1, 129.2, 130.8, 140.1, 141.4, 156.5, 157.3, 159.1. MS m/z (%): 625 (M⁺) (38), 624 (21), 592 (23), 510 (31), 467 (36), 284 (64), 210 (100), 89 (98). Anal. Calcd for C₃₁H₂₁Cl₂N₇O₄ (626.45): C, 59.44; H, 3.83; N, 15.65. Found: C, 59.47; H, 3.87; N, 15.61.

2,6-Bis[4-cyano-3-phenylcarbamoyl-1-phenyl-1H-pyrazol-5-yl]pyridine(11g). Yield 89%; Yellow solid (from ethanol/dioxan); mp 285-286 °C. IR (KBr): ν 3390 (NH), 2238 (CN) 1689(C=O) cm^{-1} . ^1H NMR (DMSO- d_6): δ 7.15-7.36 (m, 20H, ArH's), 7.82-8.15 (m, 3H, pyridine), 10.61 (s,2H, D₂O exchangeable, 2NH). MS m/z (%): 651 (M⁺) (17), 559 (8), 522 (15),

393 (15), 340 (13), 119 (20), 77 (00). Anal. Calcd for C₃₉H₂₅N₉O₂ (651.21): C, 71.88; H, 3.87; N, 19.34. Found: C, 71.85; H, 3.84; N, 19.30.

2,6-Bis[4-amino-7-methyl-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-3-yl]pyridine (13a).

Hydrazine hydrate 80% (2 ml) was added to a solution of compound **11a** (0.25 g, 5 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 3h, concentrated in vacuum, cooled, and diluted with water; the precipitate obtained was filtered, washed with ice-cold water, dried and crystallized from ethanol to afford compound **13a**. Yield 69%; yellow powder (from ethanol); mp 285-286 °C. IR (KBr): ν 3390, 3300 (NH₂) cm⁻¹. ¹H NMR (DMSO-*d*₆): δ 2.13 (s, 6H, 2CH₃), 4.3 (s, 4H, 2NH₂, D₂O exchangeable), 7.13-7.35 (m, 10H, ArH's), 7.81-8.13 (m, 3H, pyridine), MS *m/z* (%): 525 (M⁺) (61), 77 (100). Anal. Calcd for C₂₉H₂₃N₁₁ (525.57): C, 66.27; H, 4.41; N, 29.32. Found: C, 66.33; H, 4.44; N, 29.30.

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