

Synthesis of some new 2,6-bis pyridines functionalized with tetra-substituted pyrazole heterocycles

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Abstract

Several new tetra-substituted pyrazoles attached to pyridine nucleus at positions 2 and 6 were synthesized from the reactions of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) with different series of hydrazonoyl chlorides including; C-acetyl-N-aryl-hydrazonoyl chlorides (**3a-c**) and (C-ethoxycarbonyl)-N-aryl-hydrazonoyl chlorides (**12a-c**). The structures of the synthesized products were established on the basis of their elemental analysis and spectral data in addition to, the chemical behavior of the reaction products with hydrazine hydrate to afford the corresponding pyrazolo[4,3-*d*]pyridazine derivative.

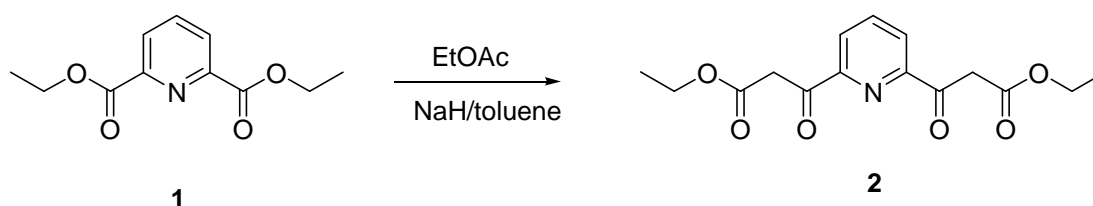
Keywords: β -Keto esters, 2,6-bis pyridine- pyrazole, pyrazolo[4,3-*d*]pyridazine

Introduction

Several compounds containing heterocycles incorporating pyridine nucleus were found to possess interesting pharmaceutical applications.¹⁻⁴ For example, several 2-pyridone derivatives such as milirinone are cardiotonic agent and has potential HIV-1 specific transcriptase inhibitor.^{5,6} Other applications of pyridines used as agrochemicals: insecticides, herbicides and fungicides.⁷ On the other hand, various pyrazole derivatives were found to possess interesting pharmacological activities that include antirheumatic, anti-inflammatory, antipyretic and analgesic properties.⁸⁻¹⁰ In view of these observations and in continuation of our interest in the synthesis of 2,6-disubstituted pyridines for different applications,¹¹⁻¹⁵ we considered it attractive to synthesize some poly substituted pyrazoles incorporated into the 2,6-pyridine moiety using 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) as starting material.

Results and Discussion

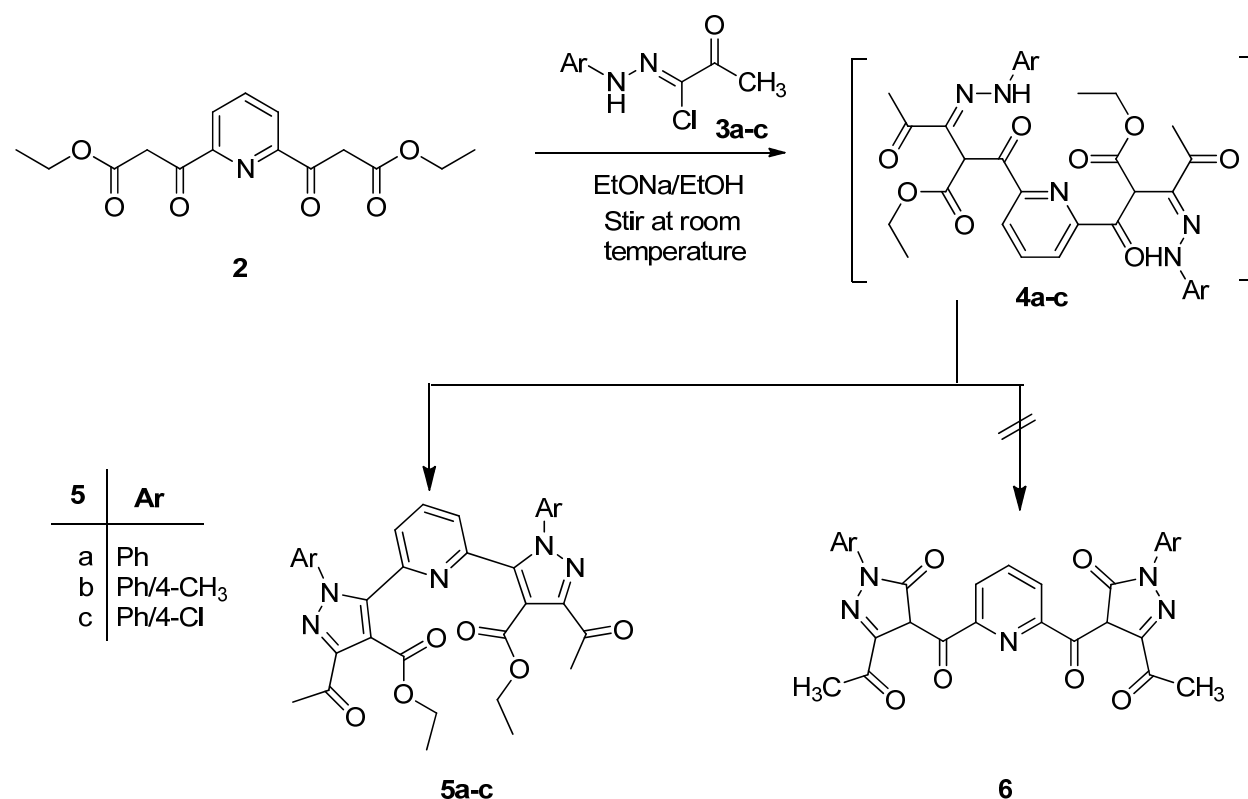
Firstly, We have prepared 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) by *Claisen* condensation of dimethyl pyridine-2,6-dicarboxylate ester (**1**) with the ethyl acetate using our procedure to synthesize pyridine-2,6-bis-(3-oxopropanenitrile)¹¹ with excellent yields (91%) that are more than the reported methods¹⁶ (Scheme 1).



Scheme 1

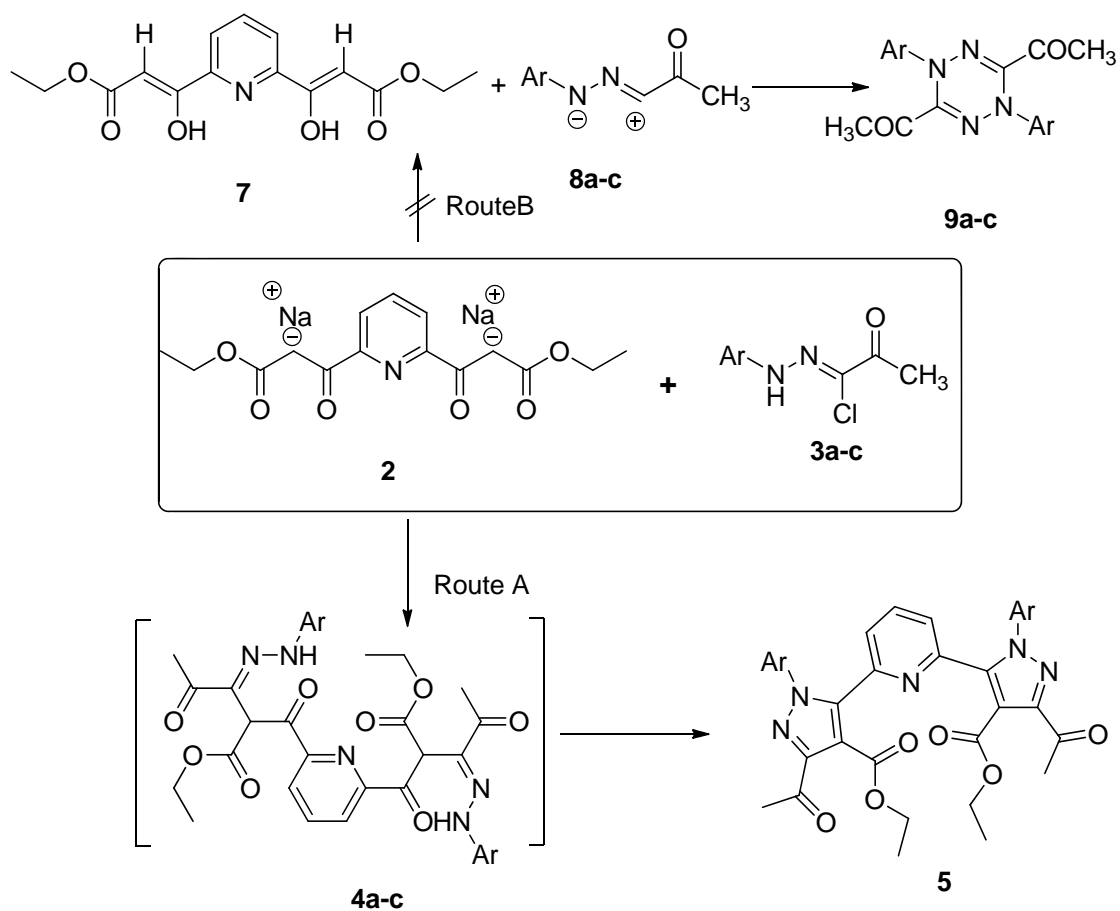
We have investigated the reactivity of compound **2** towards a variety of hydrazonoyl chlorides. Thus, Treatment of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) with *C*-acetyl-*N*-aryl-hydrazonoyl chlorides (**3a-c**) in absolute ethanol containing sodium ethoxide, yielded, in each case, only one isolable product. The identities of the isolated products were assigned as 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1*H*-pyrazol-5-yl)pyridine (**5a-c**) on the basis of their elemental analysis and spectral data (Scheme 2). For example; The IR spectra of compounds **5a-c** showed, in each case, the presence of two carbonyl stretching bands near 1730 and 1690 cm⁻¹ corresponding to ester and acetyl carbonyl groups, respectively. The ¹H NMR spectrum of **5a** taken as an example of the series synthesized, displayed triplet signals at δ 1.15, quartet signals at δ 4.21 (*J* 7.2 Hz) corresponding to CH₃ and CH₂ of the ester group, respectively and a singlet signal at δ 2.26 due to CH₃ of acetyl groups. Additionally there are multiplets at δ 7.15-7.43 and δ 7.57-8.13 due to aromatic and pyridine protons, respectively. The presence of the ester group in the IR and NMR spectra of the isolated products supported the formation of structure **5**.

Compounds **5a-c** is assumed to be formed *via* the carbanion attacks the hydrazonoyl chlorides to give the open chain intermediate hydrazones (**4a-c**) followed by intramolecular cyclization through loss of water molecules (route A) (Scheme 3). Although no attempt was made to isolate or identify the reaction intermediate, the possibilities of formation of nitrilimine intermediate (**8a-c**) from dehydrochlorination of the hydrazonoyl chlorides (**3a-c**) by the carbanion are excluded (route B), because if nitrilimine (**8**) was formed, it might dimerize to afford tetrazine (**9**) as presented in scheme 3. On the other hand, we have excluded the reaction of hydrazonoyl halide with sodium ethoxide firstly, because we have applied the reaction sequence as follow: firstly we added compound **2** to equal amount of NaOEt and left for 1/2 h that led to the formation of sodium salt of compound **2** followed by the addition of the hydrazonoyl chloride.

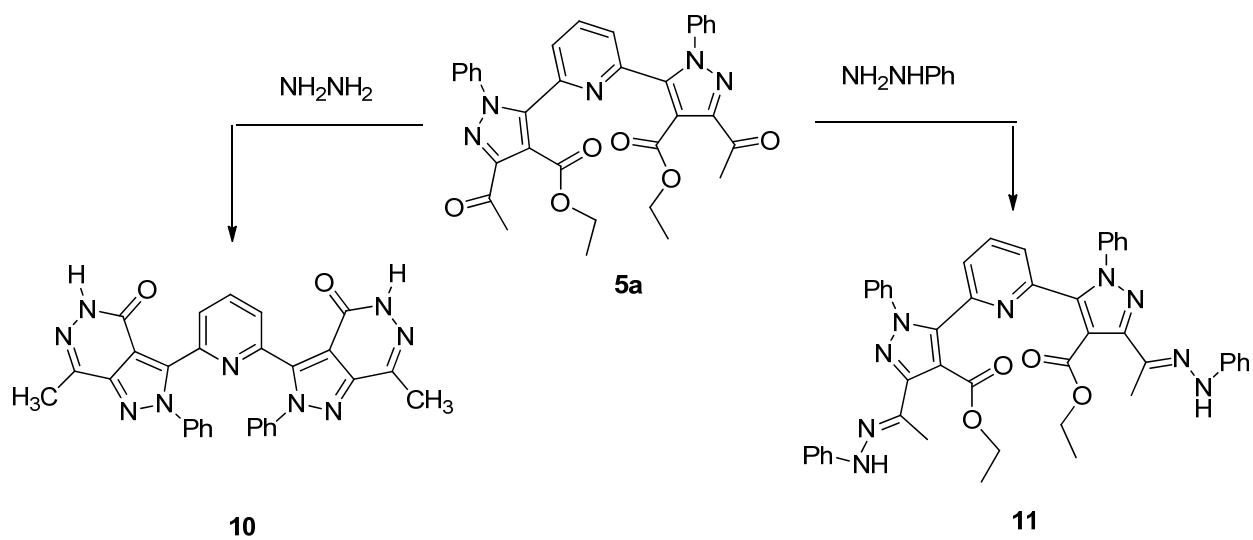


Scheme 2

The possibility of formation of **6a-c** is excluded on the basis of the spectral data and the chemical behavior of the reaction product **5a** as example with hydrazine hydrate. The corresponding pyrazolo[4,3-*d*]pyridazine derivative **10** was obtained by the reaction of **5a** with an excess of hydrazine upon refluxing in ethanol for 5h (Scheme 4). Treatment of 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-phenyl-1*H*-pyrazol-5-yl) (5a) with phenyl hydrazine in refluxing EtOH afforded a single product identified as 2,6-bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1*H*-pyrazol-5-yl)pyridine (**11**). The formation of compound **11** is assumed to proceed *via* condensation of the un-substituted nitrogen atom of phenyl hydrazine with the carbonyl function of the acetyl group and the reaction has stopped at this stage and didn't undergoes intramolecular cyclization may be due to the steric hindrance effect of the two terminals phenyl groups of the phenyl hydrazine (Scheme 4).



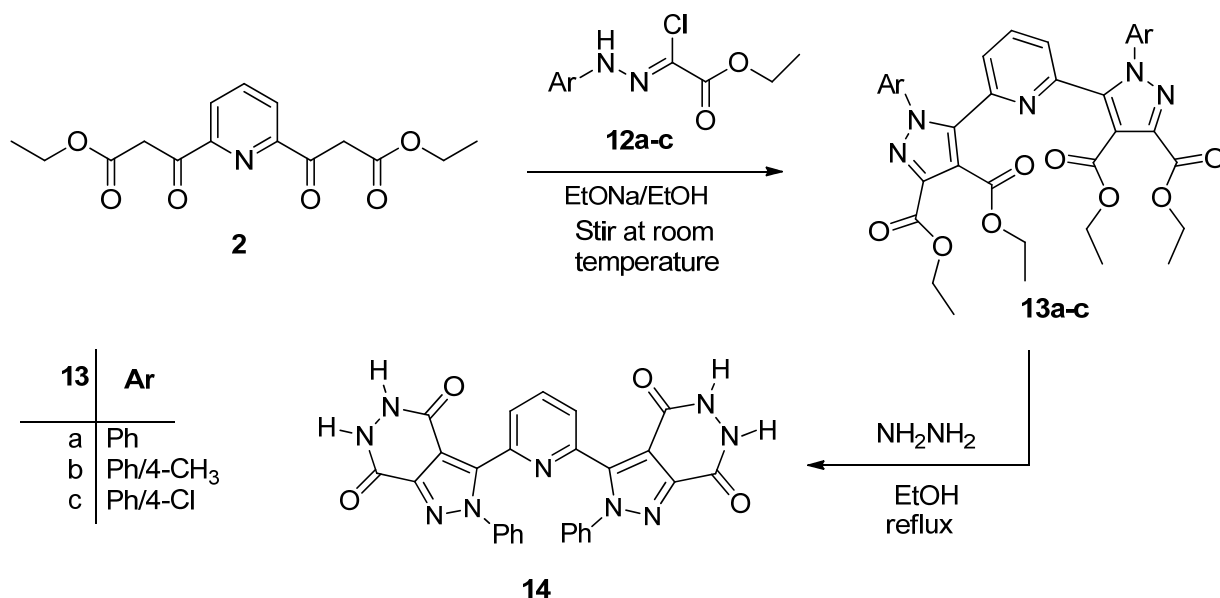
Scheme 3



Scheme 4

Also we have extended our strategy to study the reactivity of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) towards (*C*-ethoxycarbonyl)-*N*-arylhydrazonoyl chlorides (**12a-c**). Treatment of 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) with *C*-ethoxycarbonyl)-*N*-arylhydrazonoyl chlorides (**12a-c**) in absolute ethanol containing sodium ethoxide, yielded, in each case, only one isolable product. The identities of the isolated products were assigned as 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1*H*-pyrazol-5-yl)pyridine (**13a-c**) on the basis of their elemental analysis and spectral data (Scheme 5). The IR spectra of compounds **13a-c** showed, in each case, the presence of two carbonyl stretching bands near 1730 cm^{-1} corresponding to two ester groups [see Exp. Part]. The ^1H NMR spectrum of **13a** taken as example, displayed triplet signals at δ 1.13 and 1.40 in addition to, quartet signals at δ 4.13 (J 7.2 Hz) and 4.43 (J 7.2 Hz) corresponding to CH_3 and CH_2 of the ester group, respectively.. Additionally there are multiplets at δ 7.07-7.30 and δ 7.35-8.10 due to aromatic and pyridine protons, respectively. The mass spectrum of compound **13a** revealed a peak at m/z 651 corresponding to its molecular ion peak.

Finally, 2,6-bis(3,4-(diethoxycarbonyl)-1-phenyl-1*H*-pyrazol-5-yl)pyridine (**13a**) condensed with hydrazine hydrate, in refluxing EtOH and afforded the pyrazolo[4,3-*d*]pyridazine derivative **14** the structure of the later product was established on the basis of its elemental analysis and spectral data (Scheme 5).



Scheme 5

Experimental Section

General. All melting points were measured on a Gallenkamp melting point apparatus (Weiss Gallenkamp, London, UK). The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam

Ltd. Cambridge, England and Shimadzu, Tokyo, Japan, respectively). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). ^1H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform (CDCl_3) or dimethyl sulfoxide ($\text{DMSO}-d_6$). Chemical shifts are given in parts per million and were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu) 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.

Preparation of starting materials

We have prepared 2,6-bis(ethoxycarbonyl-acetyl)pyridine (**2**) by Claisen condensation of diethyl pyridine-2,6-dicarboxylate ester (**1**) with ethyl acetate in dry toluene, using NaH as a base at room temperature, and the experimental data of the product were as reported.¹⁶ 2-oxo-*N*-arylpropanehydrazonoyl chlorides (**3a-c**) and ethyl 2-(2-arylhydrazono)-2-chloroacetate derivatives (**12a-c**) were prepared following the procedures reported in the literature.^{17,18}

General procedure for the reactions of pyridine-2,6-bis(1-ethoxycarbonyl-propane-1,3-dione) (2) with the hydrazonoyl halide derivatives (3a-c) and (12a-c). 2,6-Bis(ethoxycarbonyl-acetyl)pyridine (**2**) (0.73 g, 2 mmol) was added to a stirred solution of sodium ethoxide [prepared from Na metal (0.11 g) and absolute ethanol (20 mL)]. After 30 min, the appropriate hydrazonoyl halide **3a-c** and **12a-c**, (4 mmol) was added and the reaction mixture was stirred at room temperature for additional 7-13 h. The formed solid products were collected by filtration, washed with EtOH, dried and finally recrystallized from the appropriate solvent, to afford the corresponding 2,6-bis(4-(ethoxycarbonyl)-3-acetyl-1-aryl-1*H*-pyrazol-5-yl) pyridine (**5a-c**) and 2,6-bis(3,4-(diethoxycarbonyl)-1-phenyl-1*H*-pyrazol-5-yl)pyridine (**13a-c**) derivatives, respectively.

2,6-Bis(4-(ethoxycarbonyl)-3-acetyl-1-phenyl-1*H*-pyrazol-5-yl)pyridine (5a). Yield (82 %); pale yellow crystals (EtOH); IR (KBr): ν 1732, 1694 ($2\text{C}=\text{O}$) cm^{-1} . ^1H NMR (CDCl_3): δ 1.15 (t, 6H, 2CH_3 J 7.2 Hz), 2.62 (s, 6H, 2CH_3), 4.21 (q, 4H, 2CH_2 , J 7.2 Hz), 7.15-7.43 (m, 10H, Ar-H), 7.57-8.02 (t, 1H, pyridine-H), 8.13 (d, 2H, pyridine-H). ^{13}C NMR (CDCl_3): δ 13.7, 23.21, 63.2, 117.3, 120.0, 121.3, 122.31, 126.14, 129.2, 139.1, 141.4, 145.2, 156.5, 168.11, 185.2. MS m/z (%): 591 [M^+] (37), 544 (100), 499 (22), 431 (17), 388 (23), 252 (26), 77 (79). Analysis Calcd for $\text{C}_{33}\text{H}_{29}\text{N}_5\text{O}_6$ (591.61): C, 67.00; H, 4.94; N, 11.84. Found: C, 66.97; H, 4.97; N, 11.81.

2,6-Bis(4-(ethoxycarbonyl)-3-acetyl-1-(4-methylphenyl)-1*H*-pyrazol-5-yl)pyridine (5b). Yield (78 %); yellow crystals (EtOH); mp: 206-208 °C. IR (KBr): ν 1731, 1699 ($2\text{C}=\text{O}$) cm^{-1} . ^1H NMR (CDCl_3): δ 1.08 (t, 6H, 2CH_3 J 7.3 Hz), 2.51 (s, 6H, 2CH_3), 2.81 (s, 6H, 2CH_3), 4.17 (q, 4H, 2CH_2 , J 7.3 Hz), 7.08-7.37 (m, 8H, Ar-H), 7.56-7.95 (t, 1H, pyridine-H), 8.09 (d, 2H, pyridine-H). ^{13}C NMR (CDCl_3): δ 14.1, 20.11, 23.81, 61.12, 117.2, 120.0, 121.2, 122.31, 126.28, 130.2, 136.11, 139.2, 141.15, 145.12, 156.11, 168.17, 185.12. MS m/z (%): (619) [M^+] (31), 572

(77), 530 (100), 484 (13), 287(16), 91 (62). Analysis Calcd for $C_{35}H_{33}N_5O_6$ (619.67): C, 67.84; H, 5.37; N, 11.30. Found: C, 67.77; H, 5.33; N, 11.39.

2,6-Bis(4-(ethoxycarbonyl)-3-acetyl-1-(4-chlorophenyl)-1H-pyrazol-5-yl)pyridine (5c). Yield (86 %); pale yellow crystals (EtOH/dioxane); mp: 198-199 °C. IR (KBr): ν 1731, 1698 (2C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.10 (t, 6H, 2CH₃ J 7.4 Hz), 2.71 (s, 6H, 2CH₃), 4.11 (q, 4H, 2CH₂, J 7.4 Hz), 7.17-7.39 (m, 8H, Ar-H), 7.61-8.01 (t, 1H, pyridine-H), 8.15 (d, 2H, pyridine-H). ^{13}C NMR ($CDCl_3$): δ 14.2, 25.23, 61.22, 116.13, 120.11, 121.23, 125.31, 126.44, 130.2, 137.1, 142.40, 146.12, 155.15, 168.11, 188.21. MS m/z (%): 660 [M^+] (5), 644 (23), 586 (31), 324 (15), 291 (32), 263 (5), 152 (100), 111 (75), 77 (40). Analysis Calcd for $C_{33}H_{27}Cl_2N_5O_6$ (660.5): C, 60.01; H, 4.12; N, 10.60. Found: C, 60.21; H, 4.29; N, 10.75.

2,6-Bis(4,5-dihydro-7-methyl-4-oxo-2-phenyl-2H-pyrazolo[4,3-*d*]pyridazin-3-yl) pyridine (10). Hydrazine hydrate 80% (3 mL) was added to a solution of compound **5a** (0.6 g, 1 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 9 h, concentrated in vacuum, and cooled. The precipitate obtained was filtered, washed with EtOH, dried and finally recrystallized from ethanol to afford pale yellow crystals of compound 2,6-bis(4,5-dihydro-7-methyl-4-oxo-2-phenyl-2H-pyrazolo[4,3-*d*]pyridazin-3-yl) pyridine (**10**). Yield (80%); colorless crystals (EtOH/dioxane); mp: 298-300 °C. IR (KBr): ν 3191 (NH), 1664 (C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.24 (s, 6H, 2CH₃), 7.10-7.25 (m, 10H, Ar-H), 7.74-8.00 (t, 1H, pyridine-H), 8.15 (d, 2H, pyridine-H), 9.31(s, 2H, 2NH). ^{13}C NMR ($CDCl_3$): δ 20.13, 95.21, 115.21, 120.21, 122.32, 123.21, 125.11, 128.11, 138.11, 139.71, 144.61, 155.21. MS m/z (%): 527 [M^+] (79), 469 (17), 264 (15), 77 (100). Analysis Calcd for $C_{29}H_{21}N_9O_2$ (527.54): C, 66.03; H, 4.01; N, 23.90. Found: C, 66.10; H, 3.97; N, 23.94.

2,6-Bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1H-pyrazol-5-yl)pyridine (11). A mixture of compound **5a** (0.6 g, 1 mmol) and phenyl hydrazine (0.22 g, 2 mmol), in EtOH (10 mL), was refluxed for 10h. The formed solid after cooling was filtered off, washed with EtOH, dried and finally recrystallized from EtOH to afford white powder of 2,6-bis(4-(ethoxycarbonyl)-1-phenyl-3-(1-ethylidene-2-phenylhydrazino)-1H-pyrazol-5-yl)pyridine (**11**). Yield (86%); colorless crystals (EtOH); mp: 230-232 °C. IR (KBr): ν 3298 (NH), 1710 (C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.04 (t, 6H, 2CH₃ J 7.3Hz), 2.36 (s, 6H, 2CH₃), 4.13 (q, 4H, 2CH₂, J 7.3 Hz), 6.84-7.32 (m, 20H, Ar-H), 7.46 (s, 2H, 2NH, D₂O exchangeable), 7.55-7.68 (t, 1H, pyridine-H), 8.01 (d, 2H, pyridine-H). ^{13}C NMR ($CDCl_3$): δ 12.11, 15.22, 59.21, 111.31, 116.21, 119.12, 120.32, 122.22, 125.41, 126.11, 128.34, 129.11, 130.14, 139.56, 144.11, 146.21, 155.11, 163.54. MS m/z (%): 772 (10), 771 [M^+] (3), 724 (10), 679 (63), 663 (51), 339 (13), 77 (100). Analysis Calcd for $C_{45}H_{41}N_9O_4$ (771.86): C, 70.02; H, 5.35; N, 16.33. Found: C, 70.12; H, 5.45; N, 16.39.

2,6-Bis(3,4-(diethoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl)pyridine (13a). Yield (86%); yellow crystals (EtOH); mp: 118-119 °C. IR (KBr): ν 1725, 1720 (2C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.13 (t, 6H, 2CH₃ J 7.1 Hz), 1.40 (t, 6H, 2CH₃ J 7.3 Hz), 4.13 (q, 4H, 2CH₂, J 7.1 Hz), 4.43 (q, 4H, 2CH₂, J 7.3Hz), 7.07-7.30 (m, 10H, Ar-H), 7.35-7.77 (t, 1H, pyridine-H), 8.10 (d, 2H, pyridine-H). ^{13}C NMR ($CDCl_3$): δ 12.21, 13.17, 60.11, 63.21, 116.13, 121.0, 122.11,

122.31, 125.44, 128.12, 131.1, 139.61, 144.14, 145.22, 157.15, 166.11, 166.81. MS m/z (%): 651 [M^+] (25), 77 (100). Analysis Calcd for $C_{35}H_{33}N_5O_8$ (651.67): C, 64.51; H, 5.10; N, 10.75. Found: C, 64.61; H, 5.17; N, 10.70.

2,6-Bis(3,4-(diethoxycarbonyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl)pyridine (13b). Yield (76%), yellow crystals (EtOH); mp: 214-216 °C; IR (KBr): ν 1725 (2C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.12 (t, 6H, $2CH_3$ $J=7.4$ Hz), 1.51 (t, 6H, $2CH_3$ $J=7.2$ Hz), 2.43 (s, 6H, $2CH_3$), 4.23 (q, 4H, $2CH_2$, $J=7.4$ Hz), 4.41 (q, 4H, $2CH_2$, $J=7.2$ Hz), 6.95-7.29 (m, 8H, Ar-H), 7.87-8.01 (t, 1H, pyridine-H), 8.18 (d, 2H, pyridine-H). MS m/z (%): 679 [M^+] (5). Analysis Calcd for $C_{37}H_{37}N_5O_8$ (679.72): C, 65.38; H, 5.49; N, 10.30. Found: C, 65.44; H, 5.37; N, 10.36.

2,6-Bis(3,4-(diethoxycarbonyl)-1-(4-chlorophenyl)-1H-pyrazol-5-yl)pyridine (13c). Yield (86%); pale yellow crystals (EtOH); mp: 141-142 °C. IR (KBr): ν 1727, 1710 (2C=O) cm^{-1} . 1H NMR ($CDCl_3$): δ 1.11 (t, 6H, $2CH_3$ $J=7.2$ Hz), 1.51 (t, 6H, $2CH_3$ $J=7.3$ Hz), 4.23 (q, 4H, $2CH_2$, $J=7.2$ Hz), 4.41 (q, 4H, $2CH_2$, $J=7.3$ Hz), 7.01-7.39 (m, 8H, Ar-H), 7.87-7.98 (t, 1H, pyridine-H), 8.08 (d, 2H, pyridine-H). ^{13}C NMR ($CDCl_3$): δ 12.23, 13.7, 58.22, 63.21, 116.3, 120.0, 121.21, 122.31, 125.14, 129.12, 139.61, 142.14, 145.32, 158.5, 165.11, 166.2. MS m/z (%): 720 [M^+] (30), 719 (41), 718 (45), 671 (100), 597 (32), 527 (22), 456 (19), 286 (19), 216 (16), 111 (85), 75 (31). Analysis Calcd for $C_{35}H_{31}Cl_2N_5O_8$ (720.56): C, 58.34; H, 4.34; N, 9.72. Found: C, 58.44; H, 4.37; N, 9.81.

2,6-Bis(4,5,6,7-tetrahydro-4,7-dioxo-2-phenyl-2H-pyrazolo[3,4-*d*]pyridazin-3-yl)pyridine (14)

This was prepared using the same procedure as that used for compound **10**. Yield (69%); Colorless crystals (EtOH); mp: 141-142 °C. IR (KBr): ν 3320, 3172 (2NH), 1640, 1635 (2C=O) cm^{-1} . 1H NMR ($DMSO-d_6$): δ 6.88-7.39 (m, 10H, Ar-H), 7.73-7.95 (t, 1H, pyridine-H), 8.12 (d, 2H, pyridine-H), 9.5, 11.3 (s, 4H, 4NH, D_2O exchangeable). MS m/z (%): 531 [M^+] (3). Analysis Calcd for $C_{27}H_{17}N_9O_4$ (531.48): C, 61.02; H, 3.22; N, 23.72. Found: C, 61.13; H, 3.29; N, 23.51.

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