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SYNTHESIS OF SOME NEW PYRIDINE-2,6-BIS-HETEROCYCLES

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Abstract – The versatile multifunctional hitherto unreported pyridine-2,6-bis[ethyl 2-(*N*,*N*-dimethylamino)methylene-3-oxopropanoate] (**2**) was prepared by the reaction of pyridine-2,6-bis(ethyl 3-oxopropanoate) (**1**) with 1,1-dimethoxytrimethylamine. Several new pyrazole, isoxazole, pyrimidine, pyrazolo[1,5-*a*]pyrimidine, and imidazo[1,2-*a*]pyrimidine derivatives attached to pyridine ring at 2,6-positions have been synthesized by the reactions of the enaminone **2** with the appropriate nitrogen binucleophiles.

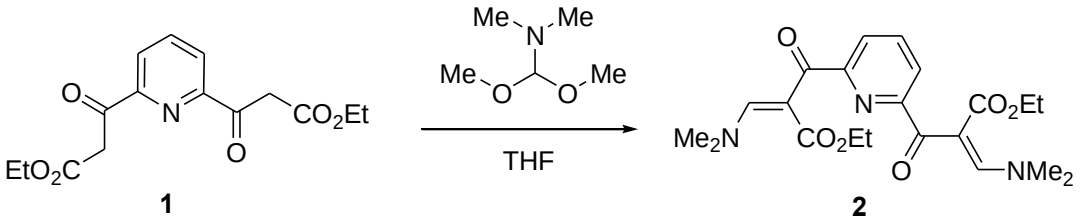
INTRODUCTION

Enaminones are reactive intermediates in which the lone pair is in conjugation with an unsaturated system, and their chemistry has received great attention as readily obtainable building blocks possessing multi-electrophilic and nucleophilic moieties.[1-5] On the other hand, functionalized pyridine derivatives are gaining a great deal of interest in medicinal and organic synthesis.[6-9] In view of these observations and in continuation of our current interest in the synthesis of poly-substituted heterocycles for biological evaluations[10-19] and our interest in the chemistry of 2,6-disubstituted pyridine derivatives,[20,21] we describe herein a facile synthesis of novel 2,6-disubstituted pyridines with functionalized azole and azine moieties by the reaction of pyridine-2,6-bis[ethyl 2-(*N*,*N*-dimethylamino)methylene-3-oxopropanoate] (**2**) with 1,2- or 1,3-binucleophiles. A facile synthesis of condensed azole and azine derivatives incorporated into positions 2 and 6 of the pyridine ring, by reaction of compound **2** with electron-rich amino-heterocycles (*viz*. aminopyrazole and 2-aminobenzimidazole), is also reported.

RESULTS AND DISCUSSION

Treatment of pyridine-2,6-bis(ethyl 3-oxopropanoate) (**1**) with 1,1-dimethoxytrimethylamine, in dry THF, afforded a yellow crystalline product identified as pyridine-2,6-bis[ethyl 2-(*N*,*N*-

dimethylamino)methylene-3-oxopropanoate] (**2**) (Scheme 1). The ^{1}H NMR spectrum of the enaminone **2** displayed a singlet signals at δ 2.83, 2.91 and 7.25 characteristics for 2*N*CH$_3$ and CH protons, respectively**.** Its mass spectrum revealed a molecular ion peak at *m/z* 417.

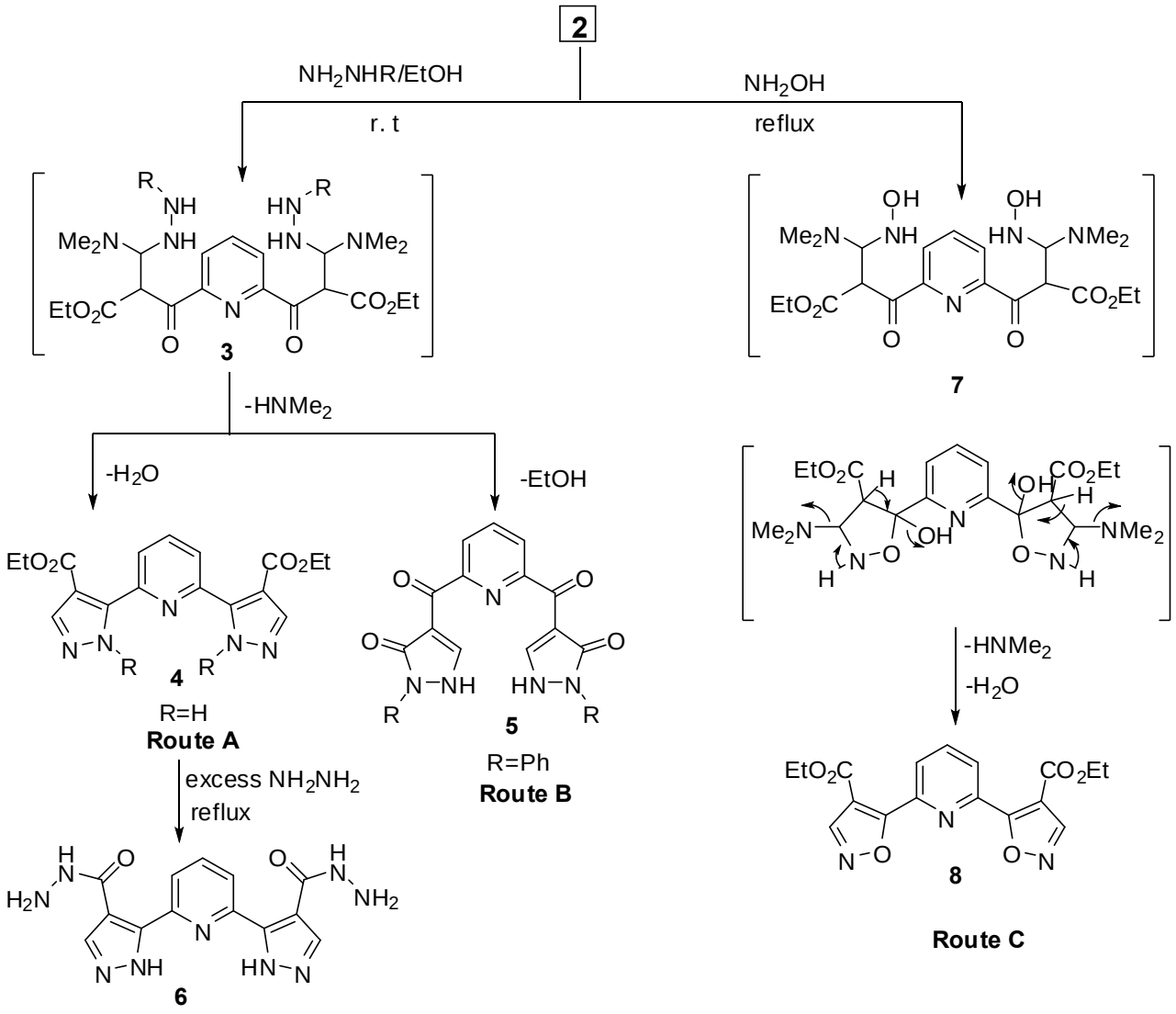


Scheme 1

The reactivity of the enaminone **2** towards some nitrogen binucleophiles was investigated. Thus, treatment of compound **2** with hydrazine afforded a product for which the two possible structures **4** and **5** can be formulated (Scheme 2). However, the spectral data of the isolated product was incomplete agreement with structure **4** (Route A, Scheme 2). The structure of compound **4** further confirmed chemically by the reaction of compound **4** with excess hydrazine, to afford the corresponding acid hydrazide **6**.

In contrast, compound **2** reacts with phenylhydrazine in refluxing ethanol to afford a yellow crystalline product identified as pyridine-2,6-bis(1,2-dihydro-3-oxo-2-phenylpyrazol-4-yl)methanone (**5**) (Route B, Scheme 2) on the basis of spectral data [see experimental part]. The formation of compounds **4** and **5** is assumed to take place *via* a Michael-type addition of the amino group of hydrazine derivative to the enamine double bond in compound **2** to form the non-isolable intermediate **3** which readily undergoes intramolecular cyclization into the pyrazole derivatives **4** or **5** *via* the loss of dimethylamine followed by the loss of water or ethanol molecules, respectively (Scheme 2). In the light of the reported results presented in Scheme **2**, the formation of the pyrazolone **5** (rather than the pyrazole carboxylate **4** in the case of *N*-aryl substituted derivative), is a surprising observation. A reasonable explanation is based on the steric factor of phenyl group in phenyl hydrazine led to the attack on the ester group in this case.

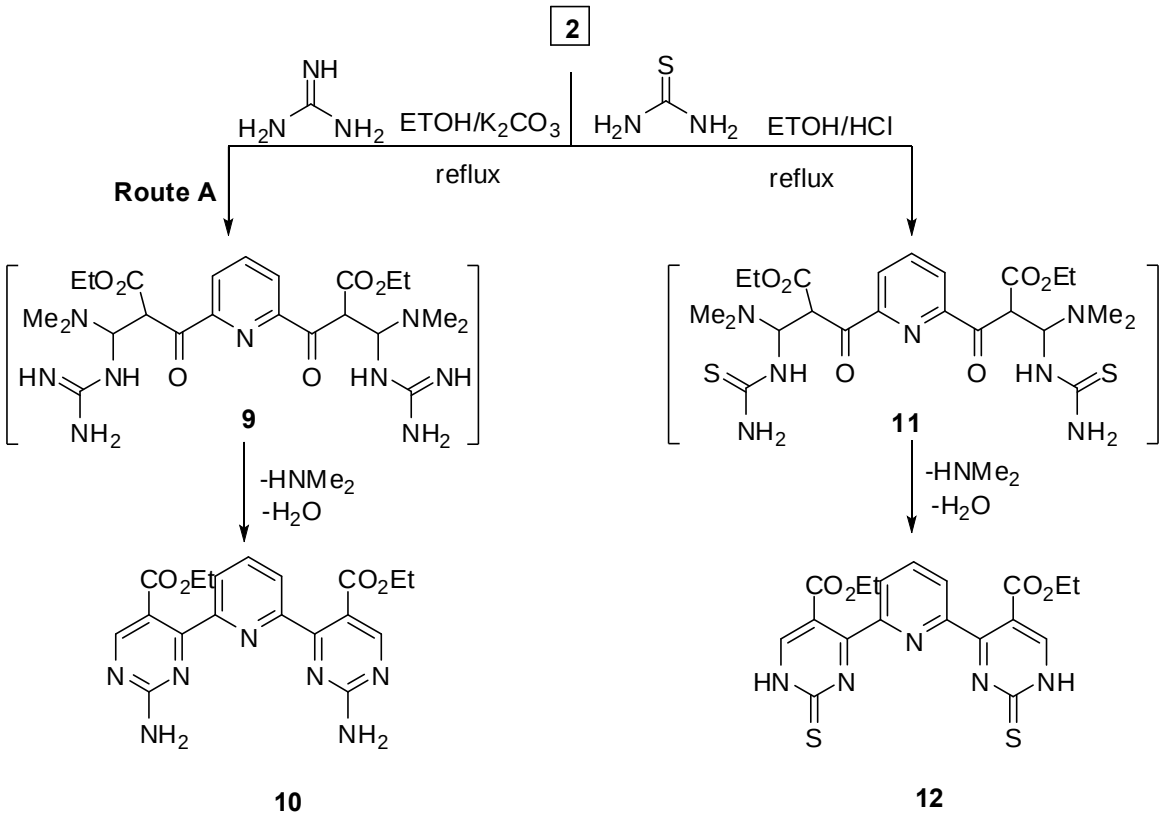
Hydrazinolysis of the pyrazole ester **4** by excess hydrazine under reflux condition for 48 h afforded the corresponding acid hydrazide (**6**) which was obtained as crystalline materials in good yields (Scheme 2). The IR spectrum of the acid hydrazide **6** revealed absorption bands at 3427-3231 and 1645 cm^{-1} corresponding to NH, NH$_2$ and amide carbonyl groups, respectively. Its ^{1}H NMR spectrum showed broad D$_2$O-exchangeable. signals at 4.25, 10.41 and 14.21 ppm corresponding to NH$_2$ and NH protons, respectively, in addition to a multiples at δ 7.21– 7.43 and 8.72 ppm characteristic for pyridine and CH pyrazole protons, respectively. The mass spectrum of the same product showed a peak at *m/z* 327 corresponding to its molecular ion.



Scheme 2

In a similar manner, the enaminone derivative **2** reacts with hydroxylamine in refluxing ethanol, to afford only one isolable product identified as 2,6-bis(4-ethoxycarbonylisoxazol-5-yl)pyridine (**8**) rather than the isomeric 2,6-bis(4-ethoxycarbonylisoxazol-3-yl)pyridine structure (Scheme 2). Compound **8** is assumed to be formed *via* Michael-type addition of the amino group of hydroxylamine to the enamine double bond in the enaminone **2** to form the non-isolable intermediate **7** which underwent intramolecular cyclization *via* elimination of dimethylamine and water molecules to afford the corresponding isoxazole derivative **8** (Route C, Scheme 2).The structure of compound **8** was assigned as the correct structure on the basis of the ^{1}H NMR spectrum of the isolated product, where a resonance for H-3 of the isoxazole ring appeared at 7.25 ppm. The isomeric 2,6-bis(4-ethoxycarbonylisoxazol-3-yl)pyridine structure was ruled out as H-5 of isoxazole would be expected to resonate at lower filed around 9.30 ppm.[22,23] The IR spectrum of compound **8** exhibited absorption band at 1728 cm^{-1} corresponding to ester carbonyl group and its mass spectrum revealed a molecular ion peak at *m/z* 357.

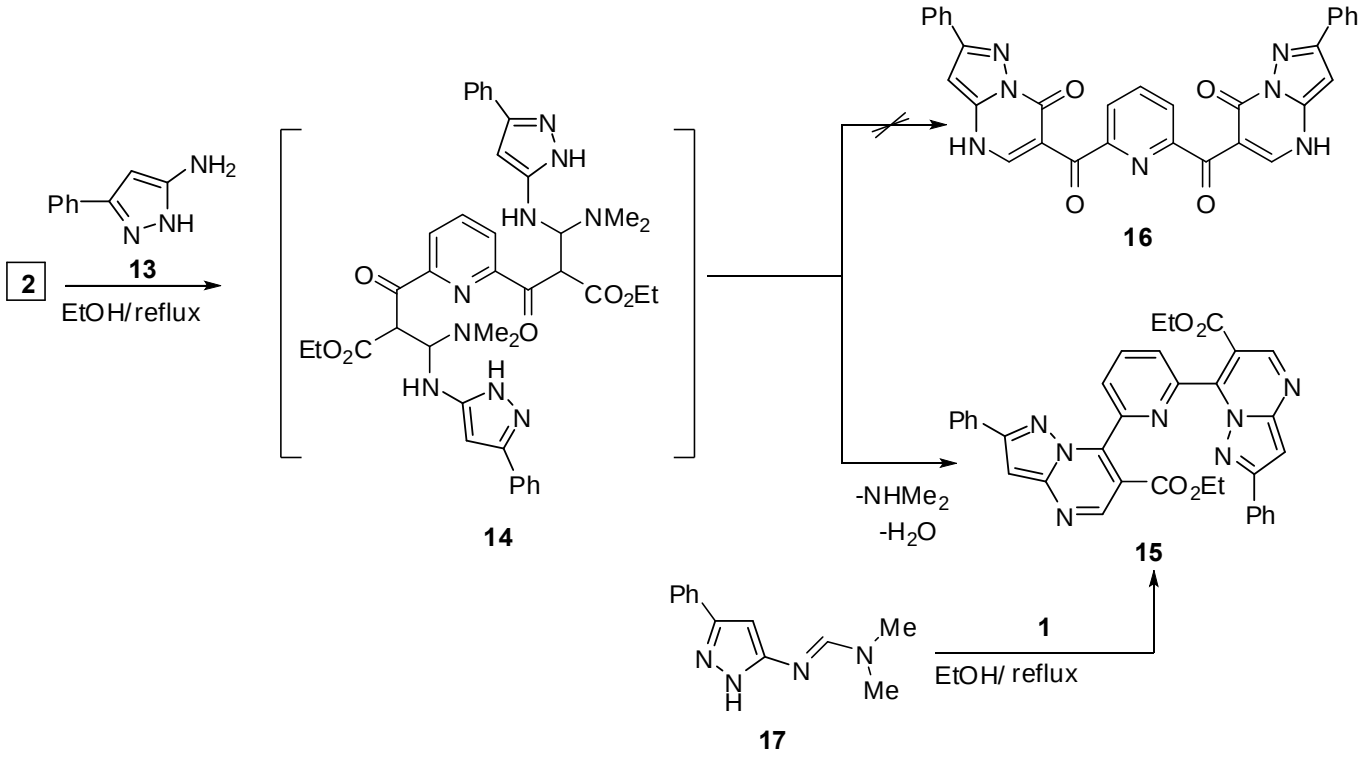
The enaminone **2** reacts also with guanidine to give a single product (as examined by TLC) identified as 2,6-bis(5-(ethoxycarbonyl)-2-aminopyrimidin-4-yl)pyridine (**10)** according to its elemental analysis and spectral data. For example, the IR spectrum of compound **10** showed amino and carbonyl absorption bands at 3396-3179 and 1710, respectively. These data are compatible with the assigned structure which seemed to be formed *via* the cyclization mode of Route A (Scheme 3). The foregoing results and our synthetic strategy towards new class of 2,6-disubstituted pyridines prompted us to investigate the behaviour of the enaminone **2** towards thiourea. Few examples of acid catalyzed dimethylamine substitution reactions of enaminone with amido-*N*-nucleophiles such as thiourea have been described in the literature,[24,25] probably due to the low nucleophilicity of amide nitrogen atoms. Thus, treatment of the enaminone **2** with excess of thiourea (6 equiv) in DMF, in the presence of HCl, afforded the corresponding pyridyl uraciles **12** (Scheme 3). The structure of the synthesized product was established on the basis of its elemental analysis and spectral data [see experimental]. Since nitrogen is a stronger nucleophile than sulphur atom in thiourea, the formation of compounds **12** can be explained on the basis of an initial Michael-type addition of NH_2 group to the enamine double bond in **2**, to afford the non-isolable thiouriedo intermediate **11** which subsequently cyclized into the pyridyl uracile **12** (Scheme 3).



Scheme 3

The behaviour of the enaminone **2** towards some heterocyclic amines as potential precursors for fused heterocyclic systems[26,27] was also investigated. Thus, treatment of the enaminone **2** with 5-amino-3-

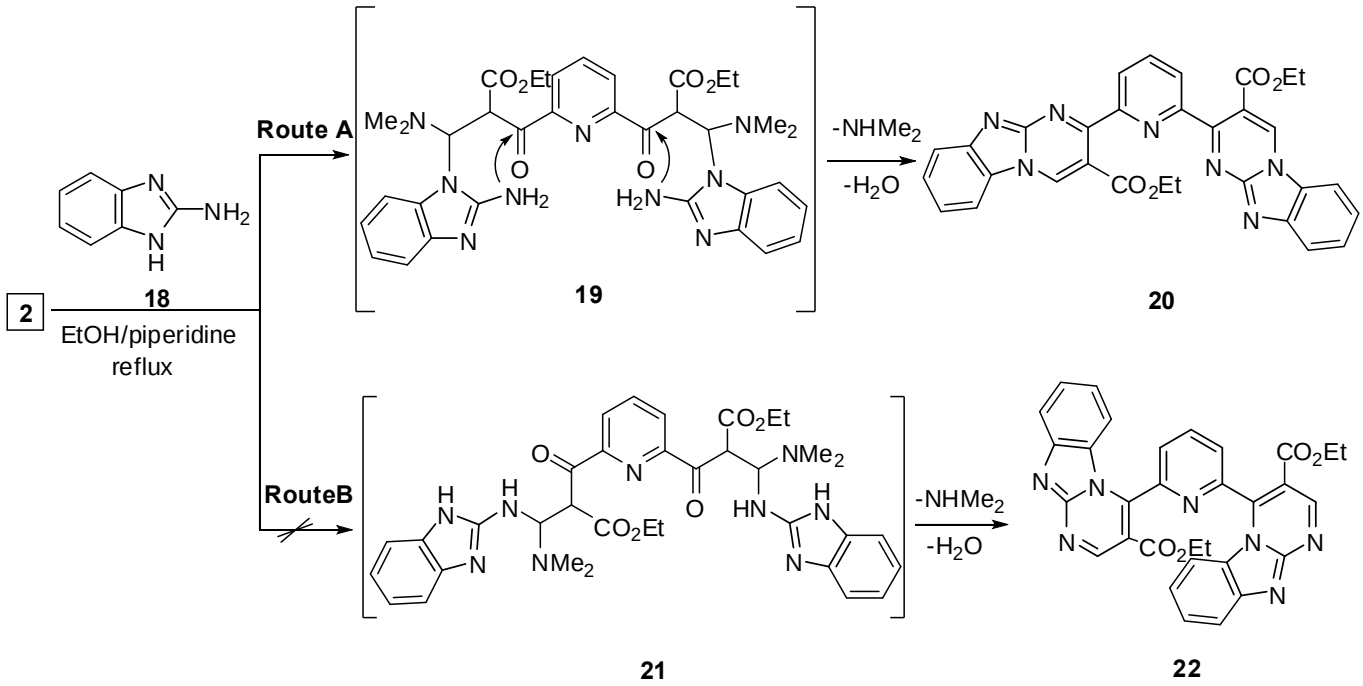
phenyl-1*H*-pyrazole (**13)**, in refluxing ethanol in the presence of a catalytic amount of piperidine, furnished a single product identified as 2,6-bis(6-ethoxycarbonyl-2-phenylpyrazolo[1,5-*a*]pyrimidin-7-yl)pyridine (**15**) (Scheme 4). Further evidence for the proposed structure **15** was obtained by an independent synthesis *via* treatment of 5-*N*-(*N*,*N*-dimethylaminomethylene)imino-3-phenyl-1*H*-pyrazole (**17)** with pyridine-2,6-bis(ethyl 3-oxopropanoate) (**1**), in refluxing ethanol which afforded a product identical in all respects (mp, mixed mp, TLC and spectra) with that obtained from the reaction of the enaminone **2** with 5-amino-3-phenyl-1*H*-pyrazole (**13**). Although the endocyclic imino group in compounds **13** is the most nucleophilic center[28-30] nevertheless, it is the most sterically hindered site.[31,32] Thus, the reaction of the enaminone **2** with 5-amino-3-phenyl-1*H*-pyrazole (**13**) is assumed to take place *via* an initial Michael-type addition of exocyclic NH_2 in **13** to the enamine double bond in **2** to afford the non-isolable intermediate **14** that undergoes intramolecular cyclization and aromatization *via* loss of both dimethylamine and water molecules to afford the isolable product **15** (Scheme 4).



Scheme 4

In contrast to its behaviour towards compound **13**, the enaminone **2** reacts with 2-aminobenzimidazole (**18**) in refluxing ethanol, under the same experimental conditions, to give a single product (as examined by TLC) which was identified as 2,6-bis(3-ethoxycarbonylbenzimidazo[1,2-*a*]pyrimidin-2-yl)pyridine (**20**) according to its elemental analysis and spectral data (Scheme **5**). The formation of compound **20** is assumed to proceed *via* an initial Michael-type addition of the endocyclic NH (imino function) in compound **18** to the activated double bond in the enaminone **2** to form the non-isolable acyclic intermediate

19 which undergoes intramolecular cyclization via elimination of dimethylamine and subsequent aromatization to afford compound **20** (Route A).



Scheme 5

The discrepancy in the behavior of compound **18** can be explained on the basis of steric factors. Thus, if the final product proceeds according to route B, the formation of compound **20** would be difficult due to steric interaction of the benzene ring of benzimidazole nucleus.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide discs on a Pye Unicam 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 automatic analyzer. All reactions were followed by TLC (Silica gel, Aluminum Sheets 60 F_{254}, Merck). Compounds **1**,[20] **13**[33-35] and **17**[36] were prepared according to literature procedures.

Pyridine-2,6-bis[ethyl 2-(N,N-dimethylamino)methylene-3-oxopropanoate] (2)

A mixture of pyridine-2,6-bis(ethyl 3-oxopropanoate) (**1**) (3.07 g, 10 mmol) and 1,1-dimethoxytrimethylamine (3.99 mL, 30 mmol) in dry THF (20 mL) was stirred at rt for 7 h. The solvent

was removed under reduced pressure, and the solid product was washed with Et_2O, filtered off, dried and finally recrystallized from EtOAc to afford brown crystals of pyridine-2,6-bis[ethyl 2-(*N*,*N*-dimethylamino)methylene-3-oxopropanoate] (**2**). Yield (3.50 g, 84%); brown crystals (from EtOAc); mp 55- 57 °C. IR (KBr, cm^{-1}): *v* 1730, 1671 (2C=O). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 6H, $2CH_3$, *J* = 7.2 Hz), 2.83 (s, 6H, $2CH_3$), 2.91 (s, 6H, $2CH_3$), 4.01 (q, 4H, $2CH_2$, *J* = 7.2 Hz), 7.25 (s, 2H, 2CH- enamine), 8.07-8.24 (m, 3H, pyridine). ^{13}C NMR ($CDCl_3$): δ 16.7, 45.2, 45.3, 61.7, 92.1, 122.7, 135.7, 151.2, 163.1, 164.5, 185. MS *m/z* (%): 417 [M^+] (12). Anal. Calcd for $C_{21}H_{27}N_3O_6$ (417.46): C, 60.42; H, 6.52; N, 10.07. Found: C, 60.32; H, 6.46; N, 10.13.

2,6-Bis(4-ethoxycarbonyl-1H-pyrazol-5-yl)pyridine (4).

A mixture of hydrazine hydrate (60%, 1.10 mL) and enaminone **2** (0.42 g, 1 mmol) in EtOH (15 mL), was stirred at rt for 4 h. The precipitate solid was collected by filtration, washed with EtOH, dried and finally recrystallized from EtOH to afford 2,6-bis(4-ethoxycarbonyl-1*H*-pyrazol-5-yl)pyridine (**4**). Yield (0.31 g, 88%), mp 217-219 °C. IR (KBr) cm^{-1}: *v* 3278 (NH), 1718 (C=O). ^{1}H NMR (DMSO-d_6): δ 1.02 (t, 6H, $2CH_3$, *J* = 7.2 Hz), 4.25 (q, 4H, $2CH_2$, *J* = 7.2 Hz), 8.01-8.10 (m, 3H, pyridine), 8.82 (s, 2H, 2CH-pyrazole), 14.21 (s, 2H, 2NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 16.3, 63.2, 107.3, 121.5, 135.7, 139.6, 149.3, 160.1, 167.2. MS *m/z* (%): 355 [M^+] (3), 275 (24), 229 (42), 171 (100). Anal. Calcd for $C_{17}H_{17}N_5O_4$ (355.35): C, 57.46; H, 4.82; N, 19.71. Found: C, 57.23; H, 4.71; N, 19.80.

Pyridine-2,6-bis(1,2-dihydro-3-oxo-2-phenylpyrazol-4-yl)methanone (5).

To a solution of the enaminone **2** (0.41 g, 1 mmol) in EtOH (10 mL), phenylhydrazine (2 mmol, 0.22 g) was added. The reaction mixture was refluxed for 5 h, then left to cool to rt. The solid precipitate was collected by filtration, washed with ethanol and dried. Recrystallization from EtOH afforded white crystals of pyridine-2,6-bis(1,2-dihydro-3-oxo-2-phenylpyrazol-4-yl)methanone (**5**). Yield (0.37 g, 85%, white crystals), mp 188-189 °C. IR (KBr) cm^{-1}: *v* 3362 (NH), 1708, 1678 (2C=O). ^{1}H NMR (DMSO-d_6): δ 6.50-7.20 (m, 10H, Ar-H), 7.30-7.97 (m, 3H, pyridine), 8.22 (s, 2H, 2CH-pyrazole), 9.98 (s, 2H, 2NH, D_2O-exchangeable). MS *m/z* (%): 451 [M^+] (60), 413 (60), 370 (50), 227 (50), 187 (70). 80 (100). Anal. Calcd for $C_{25}H_{17}N_5O_4$ (451.43): C, 66.51; H, 3.80; N, 15.51. Found: C, 66.33; H, 3.71; N, 15.41.

Pyridine-2,6-bis(1H-pyrazol-3-yl-4-carbohydrazide) (6).

To a solution of diethyl 2,6-bis(4-ethoxycarbonyl-1*H*-pyrazol-5-yl)pyridine (**4**) (2 mmol, 0.71 g) in EtOH, hydrazine hydrate (80%, 4 mL) was added. The reaction mixture was refluxed for 48 h then was allowed to cool and the precipitate product was filtered off, washed with EtOH, dried and finally recrystallized from DMF-MeOH to afford white crystals of pyridine-2,6-bis(1*H*-pyrazol-3-yl-4-carbohydrazide) (**6**). Yield (0.47 g, 72%), mp 278-280 °C. IR (KBr) cm^{-1}: *v* 3427-3231 (2NH, NH_2), 1645 (2C=O). ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 4H, $2NH_2$, D_2O-exchangeable), 8.01-8.10 (m, 3H, pyridine), 8.72 (s, 2H, 2CH-pyrazole), 10.41, 14.21 (s, 2H, 2NH, D_2O-exchangeable). MS *m/z* (%): 327 [M^+] (3), 261 (74), 213

(34), 202 (17), 171 (100), 127 (5). Anal. Calcd for $C_{13}H_{13}N_9O_2$ (327.3): C, 47.70; H, 4.00; N, 38.52. Found: C, 47.81; H, 4.11; N, 38.62.

Reaction of pyridine-2,6-bis(ethyl 2-(N,N-dimethylamino)methylene-3-oxopropanoate) (2) with hydroxylamine hydrochloride and guanidine.

General procedure: To a mixture of the enaminone (**2**) (0.41 g, 1 mmol) and hydroxylamine hydrochloride (0.14 g, 2 mmol) or guanidine hydrochloride (0.19 g, 2 mmol) in EtOH (10 mL), was added anhydrous potassium carbonate (0.28 g, 2 mmol). The resulting mixture was refluxed for 6-9 h, then allowed to cool to rt and diluted with water (30 mL). The solid product was collected by filtration, washed with water, dried and recrystallized from the proper solvent to afford compounds **8** and **10,** respectively.

2,6-Bis(4-ethoxycarbonylisoxazol-5-yl)pyridine (8).

Yield (0.24 g, 80%, reddish brown powder), mp 160-161 ^{o}C. IR (KBr) cm^{-1}: *v* 1728, (2C=O). ^{1}H NMR (DMSO-d_6): δ 1.23 (t, 6H, 2CH_3, *J* = 7.2 Hz), 4.12 (q, 4H, 2CH_2, *J* = 7.2 Hz), 7.25 (s, 2H, 2CH-isoxzaole-H) 7.85-8.10 (m, 3H, pyridine). MS *m/z* (%): 357 [M^+] (3), 301 (12), 292 (19), 245 (50), 220 (50), 187 (37), 149 (86), 105 (54), 77 (70), 57 (100). Anal. Calcd for $C_{17}H_{15}N_3O_6$ (357.32): C, 57.14; H, 4.23; N, 11.76. Found: C, 57.41; H, 3.84; N, 12.42.

2,6-Bis(5-(ethoxycarbonyl)-2-aminopyrimidin-4-yl)pyridine (10).

Yield (0.33 g, 80%, brown powder), mp 251-253 ^{o}C. IR (KBr) cm^{-1}: *v* 3396-3179 (NH_2), 1710 (C=O). ^{1}H NMR (DMSO-d_6): δ 1.13 (t, 6H, 2CH_3, *J* = 7.1 Hz), 3.34 (q, 4H, 2CH_2, *J* = 7.1 Hz), 4.34 (br, 4H, 2NH_2, D_2O-exchangeable), 7.44-8.09 (m, 3H, pyridine), 8.55 (s, 2H, 2CH, pyrimidine-H), MS *m/z* (%): 409 [M^+] (2), 364 (19), 319 (50), 265 (100), 224 (37), 160 (86). Anal. Calcd for $C_{19}H_{19}N_7O_4$ (409.4): C, 55.74; H, 4.68; N, 23.95. Found: C, 55.61; H, 4.58; N, 23.75.

2,6-Bis(5-(ethoxycarbonyl)-1,2-dihydro-2-thioxopyrimidin-4-yl)pyridine (12).

To a solution of enaminone **2** (0.41 g, 1 mmol) and thiourea (0.45 g, 6 mmol) in DMF, HCl (37%, 0.8 mL) was added. The reaction mixture was refluxed for 3 h then allowed to cool and treated with cold water. The precipitate solid product was filtered off, washed with cold water, dried and finally recrystallized from EtOH to afford red crystals of compound **12**. Yield (0.30 g, 67%), mp 178-179 ^{o}C. IR (KBr) cm^{-1}: *v* 3414 (NH), 1711 (C=O). ^{1}H NMR (DMSO-d_6): δ 1.14 (t, 6H, 2CH_3, *J* = 7.3 Hz), 3.71 (q, 4H, 2CH_2, *J* = 7.1 Hz), 1.91-8.52 (m, 3H, pyridine), 8.67 (s, 2H, 2CH, pyrimidine-H) 8.89 (s, 2H, 2NH, D_2O- exchangeable). MS *m/z* (%): 443 [M^+] (5), 361 (16), 326 (17), 261 (78), 189 (97), 105 (100). Anal. Calcd for $C_{19}H_{17}N_5O_4S_2$ (443.50): C, 51.46; H, 3.86; N, 15.79. Found: C, 51.23; H, 3.75; N, 15.69.

2,6-Bis(6-ethoxycarbonyl-2-phenylpyrazolo[1,5-a]pyrimidin-7-yl)pyridine (15).

Method A. A mixture of the enaminone **2** (1 mmol, 0.41g) and 5-amino-3-phenyl-1*H*-pyrazole (**13)** (0.32 g, 2 mmol) in EtOH (20 mL) was refluxed for 5 h, and then allowed to cool to rt. The solid product was collected by filtration, washed with EtOH, dried and finally recrystallized from EtOH to afford compound

15. Yield: (0.47 g, 81%). yellow crystal (EtOH), mp 178-179 °C. IR (KBr) cm^{-1}: *v* 1718 (C=O). ^1H NMR ($CDCl_3$): δ 1.29 (t, 6H, $2CH_3$, *J* = 7.2 Hz), 4.04 (q, 4H, $2CH_2$, *J* = 7.2 Hz), 7.11(s, 2H, 2CH, pyrazole-H), 7.37 (m, 10H, Ar-H), 7.85-8.32 (m, 3H, pyridine), 8.99 (s, 2H, 2CH, pyrimidine-H). MS *m/z* (%): 609 [M^+] (8), 547 (7), 417 (24), 315 (67), 271 (45), 186 (16), 149 (18), 102 (30), 76 (62). Anal. Calcd for $C_{35}H_{27}N_7O_4$ (609.63): C, 68.96; H, 4.46; N, 16.08. Found: C, 69.13; H, 4.59; N, 15.88.

Method B. A mixture of pyridine-2,6-bis(ethyl 3-oxopropanoate) (**1**)[20] (0.31 g, 1 mmol) and (*E*)-*N*,*N*-dimethyl-*N*'-(3-phenyl-1*H*-pyrazol-5-yl)formamidine (**17**) (0.43 g, 2 mmol) in EtOH (10 mL) was heated under reflux for 9 h, and then left to cool. The precipitated solid product was collected by filtration, washed with EtOH, dried, and finally recrystallized from EtOH to afford (0.41 g, 70%) of a products identical in all respect (mp, TLC, IR, NMR) with that of method A above.

2,6-Bis(3-ethoxycarbonylbenzo[4,5]imidazo[1,2-a]pyrimidin-2-yl)pyridine (20).

A mixture of the enaminone derivative **2** (0.42 g, 1 mmol) and 2-aminobenzimidazole (0.26 g, 2 mmol) in EtOH, was refluxed for 4 h then left to cool. The reaction mixture was poured into a cold solution of HCl (0.5 *N*). The precipitate product was filtered off, washed with cold water, dried and finally recrystallized from EtOH to afford yellow crystals of compound **20**. Yield (0.41 g, 74%), mp 121-122 °C. IR (KBr) cm^{-1}: *v* 1720 (C=O). ^1H NMR ($CDCl_3$): δ 1.15 (t, 6H, $2CH_3$, *J* = 7.3 Hz), 4.37 (q, 4H, $2CH_2$, *J* = 7.3 Hz), 7.29-7.43 (m, 8H, Ar-H), 7.67-8.36 (m, 3H, pyridine), 9.21 (s, 2H, 2CH, pyrimidine-H). MS *m/z* (%): 557 [M^+] (2), 529 (8), 412 (29), 237 (43), 177 (48), 125 (53), 85 (33). Anal. Calcd for $C_{31}H_{23}N_7O_4$ (557.56): C, 66.78; H, 4.16; N, 17.59. Found: C, 66.88; H, 4.33; N, 17.67.

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REFERENCES

1. F. Al-Omran, M. M, Abdel Khalik, A. A. ElKhair, and M. H. Elnagdi, *Synthesis*, 1997, 91.
2. S. Al-Mousawi, M. S. Moustafa, and M. H. Elnagdi, *ARKIVOC*, 2008, (**x**), 17.
3. A. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2003, **59**, 8463.
4. C. B. de Koning, J. P. Michael, and D. L. Riley, *Heterocycles*, 2009, **79**, 935.
5. J. Svete, *ARKIVOC*, 2006, (**vii**), 35.
6. G. Lahaus and S. W. Dittmar, Africa Patent 6 906036 (*Chem. Abstr*., 1988, **73**, 720308).
7. R. J. Hammond, B. W. Poston, I. Ghiviriga, and B. D. Feske, *Tetrahedron Lett.*, 2007, **48**, 1217.
8. P. Dorigo, R. M. Gaion, P. Belluco, D. Fraccarollo, I. Maragano, G. Bombien, F. Benelollo, L. Mostil,

and F. Orsini, *J. Med. Chem.*, 1993, **36**, 2475.

9. V. Dolle, E. C. H. Nguyen, A. M. Aubertin, A. M. Kirm, L. Andreola, G. Jamieson, L. Tarrago-Litvak, and E. Bisagni, *J. Med. Chem.*, 1995, **38**, 4679.
10. G. Mlostoń, A. Pieczonka, K. A. Ali, A. Linden, and H. Heimgartner, *ARKIVOC*, 2012, (**iii**), 181.
11. Y. N. Mabkhot, N. A. Kheder, and A. M. Farag, *Heterocycles*, 2011, **83**, 609.
12. K. A. Ali, E. A. Ragab, T. A. Farghaly, and M. M. Abdalla, *Acta Pol. Pharm. Drug Research*, 2011, **68**, 237.
13. S. A. Ghozlan, A. A. Mohammed, A. E. Amr, K. A. Ali, and A. A. Abd El-Wahab, *J. Heterocycl. Chem.*, 2011, **48**, 1103.
14. E. S. Darwish, N. A. Kheder, and A. M. Farag, *Heterocycles*, 2010, **81**, 2247.
15. A. M. Farag, A. S. Mayhoub, T. M. Abdalla, A. E. Amr, K. A. Ali, N. A. Abdel-Hafez, and M. M. Abdalla, *Arch. Pharm. Chem.*, 2010, **343**, 384.
16. M. R. Saaban, T. S. Saleh, and A. M. Farag, *Heterocycles*, 2009, **78**, 151.
17. A. E. Amr, K. A. Ali, and M. M. Abdalla, *Eur. J. Med. Chem.*, 2009, **44**, 901.
18. N. A. Kheder, Y. N. Mabkhot, and A. M. Farag, *Heterocycles*, 2008, **75**, 887.
19. K. A. Ali, Y. M. Elkholy, and A. M. Farag, *J. Heterocycl. Chem.*, 2008, **45**, 279.
20. K. A. Ali, *ARKIVOC*, 2010, (**xi**), 55.
21. K. A. Ali, M. A. Elsayed, and H. S. Abdalghfar, *ARKIVOC*, 2011, (**ii**), 103.
22. A. Z. A. Hassanien, S. A. S. Ghozlan, and M. H. Elnagdi, *J. Chin. Chem. Soc*., 2004, **51**, 575.
23. E. Dominguez, E. Ibeas, E. M. de Maigorta, J. K. Palacios, and R. SanMartin, *J. Org. Chem.*, 1996, **61**, 5435.
24. M. Deshmukh, M. Mittelbach, and H. Junek, *Monatsh. Chem.*, 1995, **126**, 91.
25. Z. Casar, B. David, S. Jurij, and S. Branko, *Tetrahedron*, 2005, **61**, 7508.
26. M. H. Elnagdi, F. A. Abdel All, and G. E. H. Elgemeie, *Heterocycles*, 1985, **23**, 3121.
27. A. M. Salaheldin, A. M. F. Oliveira-Campos, and L. M. Rodrigues, *Tetrahedron Lett.*, 2007, **48**, 8819.
28. V. Michon, C. H. du Penhoat, F. Tombret, J. M. Gillardin, F. Lepage, and L. Berthon, *Eur. J. Med. Chem.*, 1995, **30**, 147.
29. M. H. Elnagdi, N. H. Taha, E. A. Abdel All, R. M. Abdel Motaleb, and F. F. Mahmoud, *Collect. Czech. Chem. Commun.*, 1989, **24**, 1082.
30. S. M. Sherief and A. M. Hussein, *Monatsh. Chem.*, 1997, **128**, 687.
31. K. C. Joshi, Y. N. Pathak, and U. Grage, *J. Heterocycl. Chem*., 1979, **16**, 114.
32. M. A. Tarek, *Acta Chim. Slov*., 2002, **49**, 721.
33. G. R. Allen, Jr., *Org. React*., 1973, **20**, 337.
34. U. Kuecklander and W. Huehnermann, *Arch. Pharm.*, 1979, **312**, 515.

35. A. Takamizawa and Y. Hamashima, *Yakugaku Zasshi*, 1964, **84**, 1113.
36. K. M. Al-Zaydi, M. A. Al-Shiekh, and E. A. Hafez, *J. Chem. Res*., 2000, (S), 13 (M), 173.