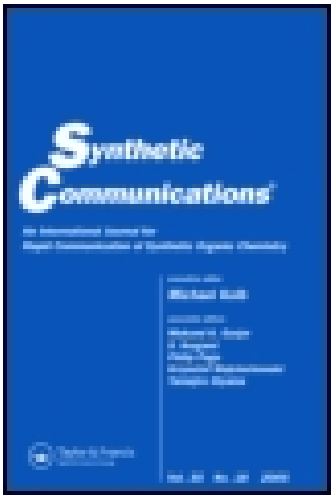

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Convenient Synthesis of Polyaza-3,4-bis(heteroaryl)pyrazoles

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CONVENIENT SYNTHESIS OF POLYAZA-3,4-BIS(HETEROARYL)PYRAZOLES

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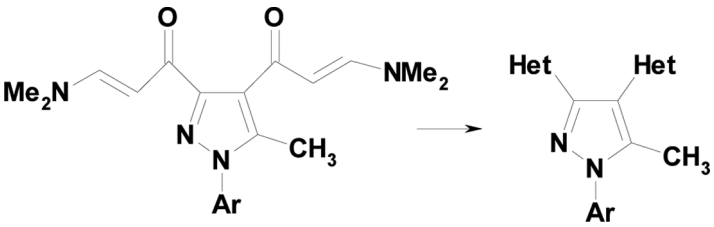
GRAPHICAL ABSTRACT



Abstract *Reactions of a new series of bis-enaminones with some N- and C-nucleophiles proved to be convenient routes for syntheses of a variety of novel 3,4-bis(heteroaryl) pyrazoles. The structures of the compounds were elucidated on the basis of their spectral and elemental analyses and by alternative synthesis wherever possible.*

Keywords Enaminones; heterocycles; hydrazonoyl halides; pyrazoles

INTRODUCTION

Enaminones **I** have been extensively studied by numerous research groups all over the world because they have proved to be versatile precursors for syntheses of many heterocycles. At present, there are several review articles covering the various aspects of their chemistry.[1] In contrast, bis-enaminones of the general formula **II**, especially where R is a heteroaryl moiety, have received much less attention.[2] In conjunction with our recent work[3] on heteroaryl-enaminones derived from hydrazonoyl halides, we extended our studies to explore the utility of such halides as precursors for synthesis of ter-heterocycles of type **III**, which have not been reported hitherto. The interest in synthesis of such ter-heterocycles is because many synthetic pyrazole derivatives have found uses in pharmaceutical, agrochemical, and photographic fields.[4–6] In this article, we report the results of our study of the reactions of the bis-enaminones **IV** ($R=CH_3$; $Ar=XC_5H_4$) with some N- and C-nucleophiles (Chart 1).

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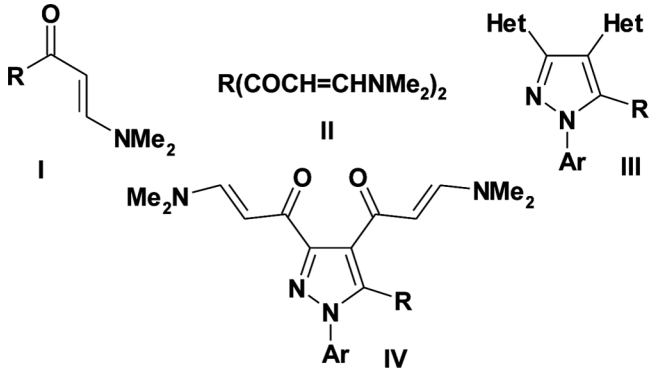
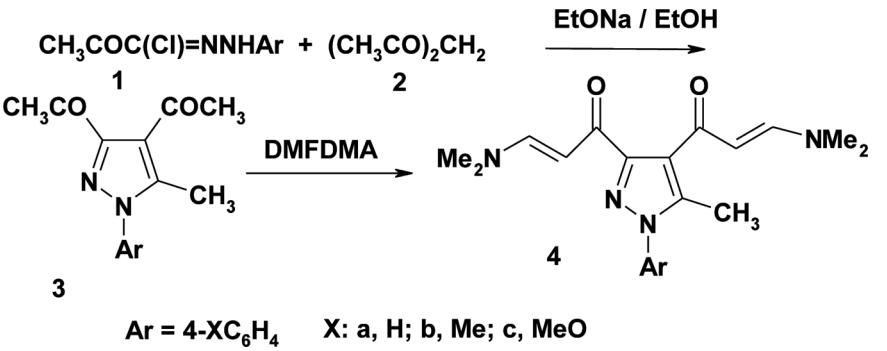


Chart 1.

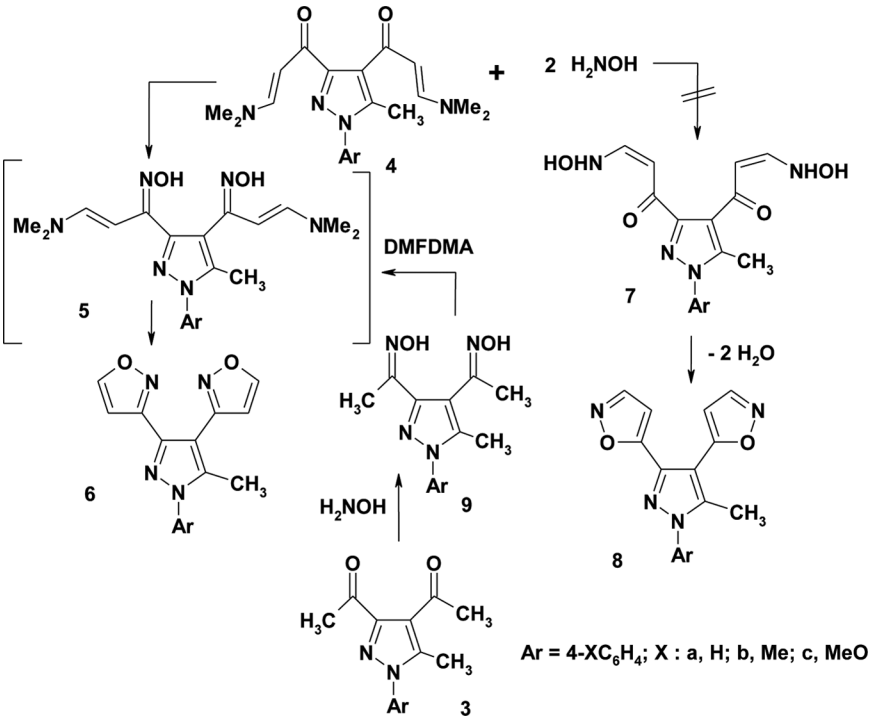
RESULTS AND DISCUSSION

The precursor *bis*-enaminones **4** were prepared by condensation of the respective 3,4-bis(acetyl)pyrazole derivatives **3**, each with dimethylformamide dimethylacetal (DMF-DMA), as previously described from our laboratory (Scheme 1).[7]

When each of the bis-enaminones **4a–c** was refluxed with hydroxylamine hydrochloride in ethanol in the presence of ammonium acetate, it yielded a single product identified as the respective 3,4-bis(isoxazol-3-yl)pyrazole **6** rather than its bis(isoxazol-5-yl)pyrazole **8** (Scheme 2). The assigned structure **6** was confirmed by an alternative synthesis of **6b** as a representative example of the series prepared. Thus, reaction of the bis-oxime **9b**, prepared from **3b** and 2 equivalents of hydroxylamine hydrochloride in refluxing ethanol in the presence of potassium hydroxide, with DMF-DMA in refluxing xylene, gave a product that proved identical in all respects to **6b** isolated from reaction of **4b** with hydroxylamine hydrochloride. On the basis of this finding, the other isomeric structure **8** was discarded. The structures of the products **6** were further established by their spectra. For example, their ^{1}H NMR spectra showed in each case two doublet signals near δ 6.83 and 8.42 with $J = 2.1$ Hz assignable to the isoxazole ring protons, namely H-4 and H-5, respect-



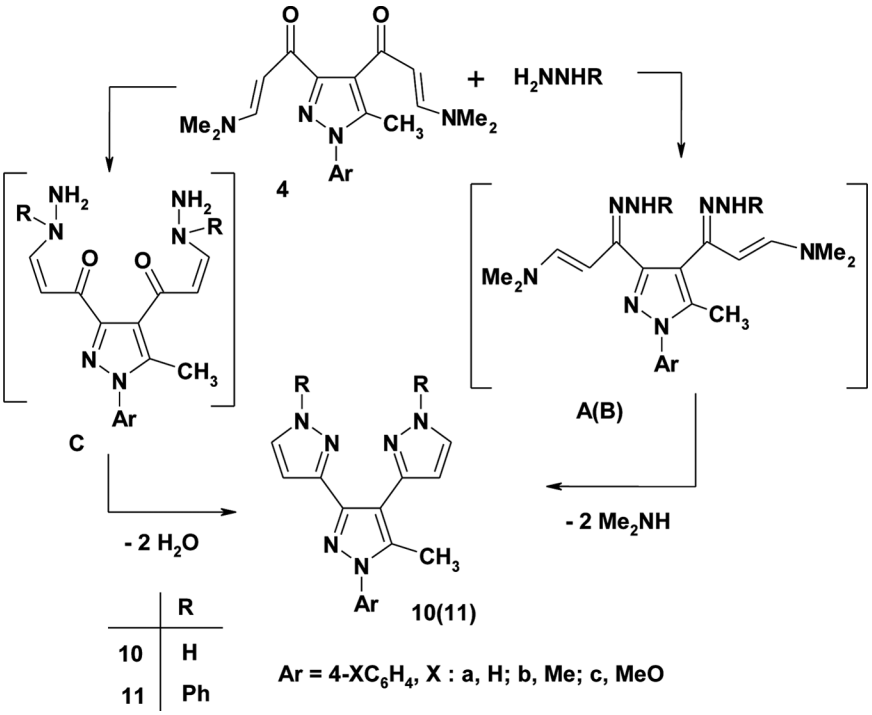
Scheme 1.



Scheme 2.

ively. Their mass spectra showed, in addition to the molecular ion peak, a fragment ion peak at m/z 68 corresponding to the isoxazolyl radical cation. To account for the reformation of the products **6**, it is assumed, as depicted in Scheme 2, that reaction of **4** with hydroxylamine starts with condensation to give **5** as intermediate, which undergoes *in situ* cyclization via elimination of dimethylamine to give **6** as end products. This sequence is compatible with literature reports on reactions of hydroxylamine hydrochloride with mono-enaminones, which afford the respective isoxazol-3-yl derivatives.[8]

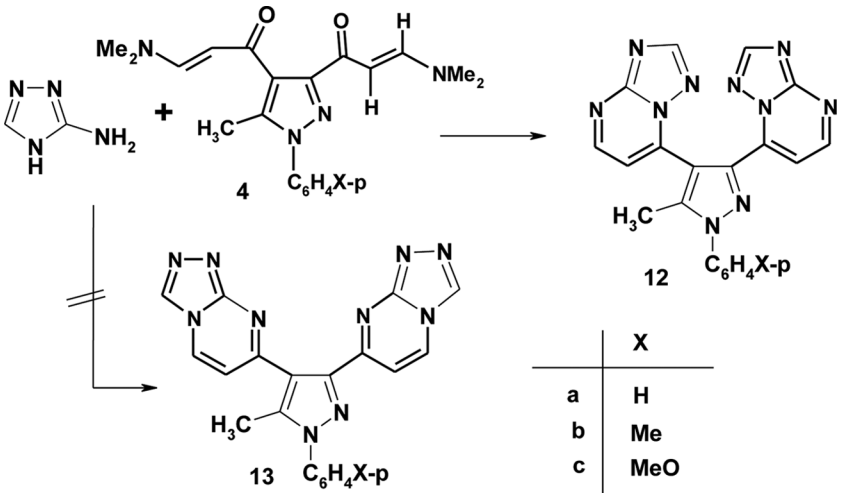
The bis-enaminones **4** reacted similarly with hydrazine hydrate and phenylhydrazine in refluxing ethanol to afford the respective 3,3′:4,3″-terpyrazoles **10** and **11** (Scheme 3). The structures of the latter products were elucidated on the basis of their spectral and elemental analysis data. For example, their IR spectra revealed the absence of the CO bands present in the spectra of the starting bis-enaminones **4**. In addition, the spectra of **10** revealed a broad NH band in the region ν 3400–3200 cm^{-1}. Also, the ^1H NMR spectra showed, in each case, two doublet signals in the regions δ 6.39–6.42 and 7.66–7.82 with the same coupling constant $J = 7$ Hz assignable to H-4 and H-5 of the pyrazole ring residues, respectively. Similarly, the ^1H NMR spectra of the products **11a–c** showed the signals of such protons as two doublet signals near δ 6.73 and 8.35 with the same coupling constant $J = 7$ Hz. Furthermore, the ^1H NMR spectra of **10** exhibit a broad singlet (D_2O-exchangeable) at δ 13.0 due to the NH proton resonance.



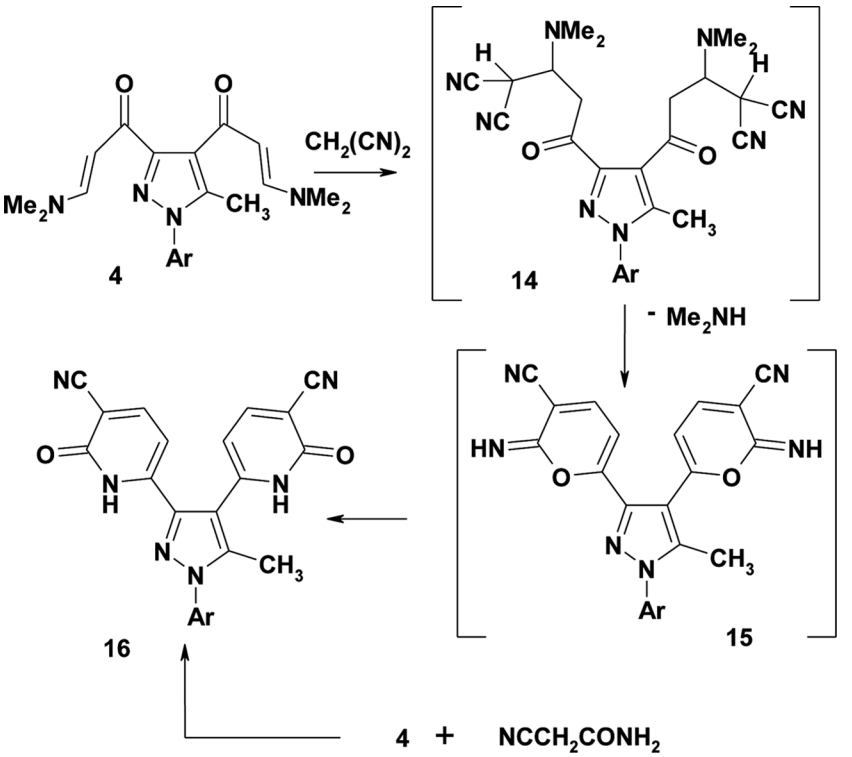
Scheme 3.

The reactivity of the bis-enaminones **4** toward 3-amino-1,2,4-triazole was next examined to shed some light on its site selectivity, as such a reaction can theoretically lead to either the 1,2,4-triazolo[1,5-*a*]pyrimidine **12** and/or its [4,3-*a*] isomer **13** (Scheme 4). In our hands, reaction of **4a–c** with 3-amino-1,2,4-triazole in acetic acid under reflux yielded, in each case, only one isolable product. The isolated products were identified as 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **12a–c** and not their 1,2,4-triazolo[4,3-*a*]pyrimidine isomers **13a–c** on the basis of their ^{1}H NMR spectra (Scheme 4). For example, their ^{1}H NMR spectra revealed in each case two doublet signals near δ 7.79 and 9.27 with $J = 9$ Hz assignable to the two vicinal protons H-6 and H-7 of the pyrimidine ring residue in addition to a singlet signal at δ 8.79 due to the H-2 proton. Such assignments are consistent with literature reports on ^{1}H NMR spectra of 1,2,4-triazolo[1,5-*a*]pyrimidine and its [4,3-*a*] isomers.[9] To account for the formation of the products **12**, it is suggested that the studied reactions start with Michael-type addition of the exocyclic NH_2 group of the amine to the activated double bond of **4** followed by *in situ* tandem elimination of dimethylamine and dehydrative cyclization by condensation of the cyclic NH group with the enone moiety (Scheme 4).

Next, we examined the reactions of bis-enaminones **4** with some C-nucleohiles. In our hands, reaction of malononitrile with each of the enaminones **4a–c** in refluxing glacial acetic acid in the presence of ammonium acetate gave rise to a single product that proved to be the corresponding 3,4-bis(5-cyano-6-oxo-1*H*-pyridin-2-yl)-1-aryl-5-methylpyrazole **16** (Scheme 5). The structures of the latter products were



Scheme 4.

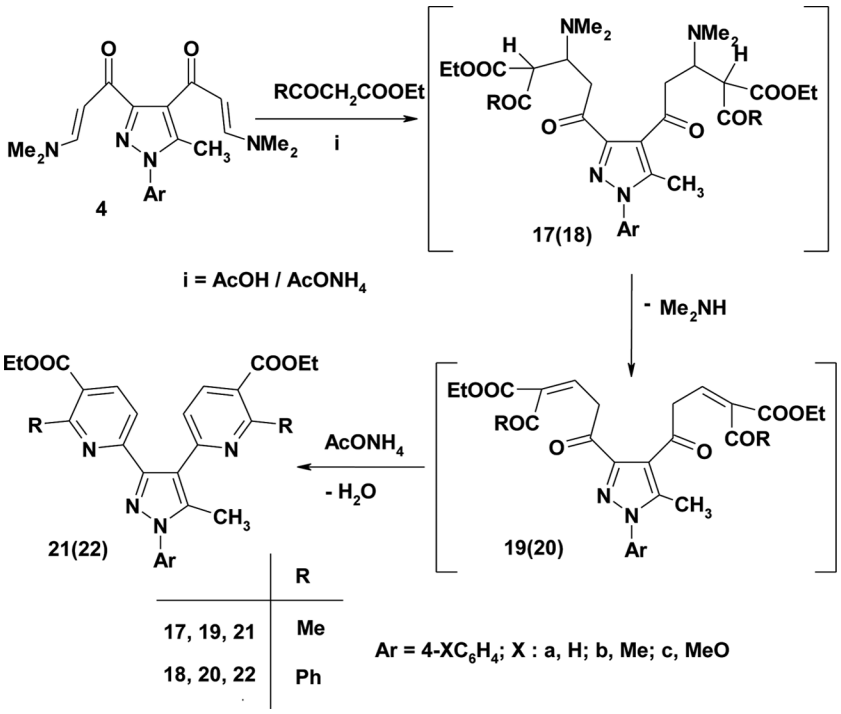


Scheme 5.

compatible with their spectral and elemental analytical data. Thus, their IR spectra showed the presence of NH, CN, and CO group stretching bands near υ 3310, 2221, and 1658 cm^{-1}, respectively. The ^1H NMR spectra revealed two doublet signals near δ 8.29 (d, 2H, $J = 8$ Hz, pyridine-H-3) and 8.19 (2H, 2H, $J = 8$ Hz, pyridine-H-4). In addition, the spectra showed a singlet at δ 12.5 due to the NH proton resonance. To account for the formation of **16**, it is suggested by analogy to reactions of malononitrile with mono-enaminones, that reaction of **4** with malononitrile starts with a Michael addition to yield the respective adduct **14**, followed by tandem *in situ* cyclization and elimination of dimethylamine to give the iminopyran **15** as intermediate. The latter isomerizes through Dimroth-type rearrangement under the reaction conditions to afford **16** as end product.

The assigned structure **16** is further evidenced by an alternative synthesis of **16a** as an example of the series prepared. Thus, reaction of **4a** with cyanoacetamide in refluxing dry toluene afforded a product that proved identical in all respects with that one obtained from reaction of **4a** with malononitrile.

When a mixture of ethyl acetoacetate and each of the bis-enaminone **4a–c** was refluxed for 30 h in glacial acetic acid in the presence of ammonium acetate, it yielded, in each case, a single product. Both elemental analyses and spectral data (see Experimental) indicate that the products isolated are the respective 3,4-bis [5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-1-aryl-5-methylpyrazole **21a-c** (Scheme 6). Ethyl benzoyl acetate reacted similarly with each of **4a–c** under the same reaction



Scheme 6.

conditions and afforded the respective 3,4-bis[5-ethoxycarbonyl-6-phenyl-pyrid-2-yl]-1-aryl-5-methylpyrazoles **22a–c** (Scheme 6). A reaction pathway that accounts for the formation of the products **21** and **22** is depicted in Scheme 6. It involves initial addition of the active methylene moiety to the activated double bond of **4** to afford **17(18)** as intermediates that undergo elimination of dimethylamine to afford **19(20)**, which in turn condenses with ammonium acetate to yield the respective 3,4-bis(pyridine-6-yl)pyrazoles **21(22)** as end products (Scheme 3). The ^{1}H NMR spectra of both compounds **21** and **22** revealed, in addition to the characteristic signals for the protons of the aryl and $COOCH_2CH_3$ groups, signals at δ 7.5–7.8 (d, $J = 9\,Hz$, 2H, pyridine-H-3) and 8.2–8.3 (d, $J = 9\,Hz$, 2H, pyridine-H-4), Compunds **21** also, exhibit, in each case, two singlet signals near δ 2.88 (s, 6H, $2CH_3$) and 2.79 (s, 3H, pyrazole-5-CH_3).

CONCLUSION

The results of the present work indicate that the studied bis-enaminones are useful precursors for the synthesis of different functionalized 3,4-bis-(hetaryl)pyrazoles through their reactions with the N- and C-nucleophiles. In addition, they indicate that the studied reactions are regiospecific as they yielded, in each case, one product. The ter-heterocycles prepared are expected to be of pharmacological interest.

EXPERIMENTAL

Melting points were determined on an electrothermal Gallenkamp apparatus. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H NMR spectra were recorded on a Varian Mercury VXR300-MHz spectrometer and the chemical shifts δ are downfield from tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, and the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Compounds **3** and **4** were prepared as previously described.[7]

Synthesis of 3,4-Bis(isoxazol-3-yl)-1-aryl-5-methylpyrazoles (6a–c)

To a solution of the appropriate bis-enaminone **4** (2 mmol) in absolute ethanol was added 0.27 g, 4 mmol of hydroxylamine hydrochloride in the presence of anhydrous potassium carbonate (0.5 g). The reaction mixture was then refluxed for 5 h. The solid formed was collected by filtration and crystallized from ethanol to give the respective compound **6**. Compounds **6a–c** together with their physical constants are listed.

3,4-Bis(isoxazol-3-yl)-1-phenyl-5-methylpyrazole (6a). Red crystals, yield 0.43 g (75%), mp 176–178 °C; IR (KBr) ν_{max}/cm^{-1} 1598 (C=N). ^{1}H NMR (DMSO-d_6) δ 3.58 (s, 3H, CH_3), 6.81 (d, $J = 7$ Hz, 2H, isoxazole-H), 7.6–7.7 (m, 5H, ArH), 8.42 (d, $J = 7$ Hz, 7 Hz, isoxazole-H); MS m/z (%) 292 (M^+, 6), 291

(8), 278 (14), 277 (19), 276 (22), 248 (14), 130 (10), 118 (21), 93 (17), 89 (16), 77 (100), 68 (13), 51 (70). Anal. calcd. for $C_{16}H_{12}N_4O_2$(292.29): C, 65.75; H, 4.14; N, 19.17. Found: C, 66.15; H, 4.35; N, 19.45%.

3,4-Bis(isoxazol-3-yl)-1-(p-tolyl)-5-methylpyrazoles (6b). Pale brown crystals, yield 0.48 g (80%), mp 210–212 °C, IR (KBr) ν_{max}/cm^{-1}1588 (C=N). ^1H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 6.83 (d, $J=7$ Hz, 7H, isoxazole-H), 7.10 (d, $J=6$ Hz, 2H, ArH), 7.45 (d, $J=6$ Hz, 2H, ArH), 8.42 (d, $J=7$ Hz, 2H, isoxazole-H); ^{13}C NMR (DMSO-d_6) δ 12.1, 24.0, 103.0, 108.4, 120.5, 129.7, 129.8, 136.0, 137.0, 138.8, 148.7, 150.3, 158.5, 162.0; MS m/z (%) 308 ($M^+ + 2$, 3), 307 ($M^+ + 1$, 9), 306 (M^+, 26), 289 (30), 290 (42), 276 (15), 262 (22), 154 (12), 149 (14), 132 (23), 106 (13), 91 (60), 77 (28), 67 (13), 65 (100), 51 (55). Anal. calcd. for $C_{17}H_{14}N_4O_2$ (306.33): C, 66.66; H, 4.61; N, 18.28. Found: C, 67.00; H, 4.82; N, 18.40%.

3,4-Bis(isoxazol-3-yl)-1(p-anisyl)-5-methylpyrazoles (6c). Pale brown crystals, yield 0.51 g (80%), mp 180–182 °C: IR (KBr) ν_{max}/cm^{-1} 1598 (C=N), 1251 (C-O-C). ^1H NMR (DMSO-d_6) δ 3.53 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.83 (d, $J=7$ Hz, 2H, isoxazole-H), 7.30 – 7.42 (m, 4H, ArH), 8.42 (d, $J=7$ Hz, 2H, isoxazole-H); MS m/z (%) 324 ($M^+ + 2$, 4), 323 ($M^+ + 1$, 9), 322 (M^+, 12), 306 (100), 292 (12), 282 (22), 237 (13), 236 (24), 207 (12), 196 (11), 172 (11), 133 (13), 123 (22), 116 (22), 108 (23), 103 (16), 98 (19), 92 (33), 84 (20), 77 (80), 67 (31), 64 (74), 51 (20). Anal. calcd. for $C_{17}H_{14}N_4O_3$(322.33): C, 63.35; H, 4.38; N, 17.38. Found: C, 63.50; H, 4.45; N, 17.70%.

Alternate Synthesis of 3,4-Bis[(3-isoxazol-3-yl)-1-(4-tolyl)]-5-methylpyrazole (6b)

Hydroxylamine hydrochloride (20 mmol) and potassium carbonate (0.5 g) were added to a solution of **3b** (2.56 g, 10 mmol) in absolute ethanol (20 ml). The mixture was then refluxed for 7 h. The precipitate formed was filtered and crystallized from ethanol to afford compound **9b** as a pale orange solid, yield (2.23 g, 78%), mp 144–146 °C, IR (KBr) ν_{max}/cm^{-1} 3340, 3272 (OH), 1590 (C=N). ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.38 (s, 3H, Ar-CH_3), 3.23 (s, 3H, CH_3), 4.40 (br, 2H, 2OH), 7.32–7.42 (m, 4H, Ar-H); MS m/z (%) 286 (M^+, 0.4) 132 (10), 91 (89), 84 (65), 76 (32), 64 (100). Anal. calcd. for $C_{15}H_{18}N_4O_2$ (286.32): C, 62.92; H, 6.34; N, 19.57. Found: C, 63.10; H, 6.50; N, 19.72%.

A mixture of compound **9b** (1.43 g, 5 mmol) and DMF-DMA (1.19 g, 10 mmol) was refluxed for 20–30 h and then left to cool. Methanol was added to the cold mixture. The resulting solid was collected by filtration, washed with methanol, dried, and finally crystallized from ethanol to afford the respective **6b** (1.31 g, 86%), mp 210–212 °C, which was found identical in all respective to that compound produced from reaction of compound **4b** with hydroxylamine hydrochloride.

Compounds 10a–c and 11–c

To a solution of **4** (0.70 g, 2 mmol) in absolute ethanol (20 ml) was added 10 ml of hydrazine hydrate. The mixture was refluxed for 5 h and then cooled. The precipitate formed was filtered off and crystallized from ethanol to give the respective

compound ter-pyrazole derivatives **10a–c**. When this procedure was repeated using phenylhydrazine in lieu of hydrazine hydrate, the respective ter-pyrazoles **11a–c** were obtained.

3,4-Bis[1H-pyrazol-3-yl]-5-methyl-1-phenyl-1H-pyrazole (10a). White crystals, yield 0.49 g (85%), mp 246–248 °C: IR (KBr) ν_{max}/cm^{-1} 3318 (NH), 1593 (C=N). ^1H NMR (DMSO-d_6) δ 3.35 (s, 3H, CH_3), 6.41 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 7.60 (s, 5H, ArH), 7.82 (d, $J = 7$ Hz, 2H, Pyrazole-H5), 13.11 (s, D_2O exchangeable, 2H, NH); MS m/z (%), 292 ($M^+ + 2$, 2), 291 ($M^+ + 1$, 16), 290 (M^+, 81), 289 (43), 262 (11), 118 (12), 77 (100), 64 (10), 51 (55). Anal. calcd. for $C_{16}H_{14}N_6$(290.33): C, 66.19; H, 4.86; N, 28.95. Found: C, 66.40; H, 4.98; N, 29.31%.

3,4-Bis[1H-pyrazol-3-yl]-5-methyl-1-(4-tolyl)-1H-pyrazole (10b). White crystals, yield 0.49 g (79%), mp 264–264 °C; IR (KBr) ν_{max}/cm^{-1} 3435 (NH), 1595 (C=N). ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 6.42 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 7.38–7.45 (m, 4H, ArH), 7.66 (d, $J = 7$ *Hz*, 2H, Pyrazole-H5), 12.98 (s, D_2O exchangeable, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ 11.5, 24.0, 103.0, 108.4, 120.5, 129.7, 129.9, 130.05, 136.03, 137.0, 138.8, 146.0, 148.0; MS m/z (%) 305 ($M^+ + 1$, 20), 304 (M^+, 83), 303 (45), 130 (19), 117 (14), 104 (11), 91 (86), 77 (18), 65 (100), 51 (65). Anal. calcd. for $C_{17}H_{16}N_6$ (304.36): C, 67.09; H, 5.30; N, 27.61. Found: C, 67.40; H, 5.51; N, 27.90%.

3,4-Bis[1H-pyrazol-3-yl]-5-methyl-1-(4-anisyl)-1H-pyrazole (10c). White crystals, yield 0.48 g (82%), mp 250–252 °C: IR (KBr) ν_{max}/cm^{-1} 3430 (NH), 1589 (C=N), 1251 (C-O-C). ^1H NMR (DMSO-d_6) δ 3.34 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.39 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 7.81 (d, $J = 7$ Hz, 2H, ArH), 7.48 (d, $J = 8$ Hz, 2H, ArH), 7.81 (d, $J = 7$ Hz, 2H, Pyrazole-H5), 13.09 (s, D_2O exchangeable, 2H, 2NH); MS m/z (%) 321 ($M^+ + 1$, 24), 320 (M^+, 78), 160 (14), 115 (21), 103 (24), 94 (19), 92 (42), 77 (100), 65 (25), 51 (42). Anal. calcd. for $C_{17}H_{16}N_6O$ (320.36): C, 63.74; H, 5.03; N, 26.23. Found: C, 64.00; H, 5.36; N, 26.54%.

3,4-Bis[1-phenyl-1H-pyrazol-3-yl]-5-methyl-1-phenyl-1H-pyrazole (11a). Yellow crystals, yield 0.68 g (75%), mp 218–220 °C; IR (KBr) ν_{max}/cm^{-1} 1593 (C=N). ^1H NMR (DMSO-d_6) 3.46 (s, 3H, CH_3), 6.83 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 7.58 (m, 15H, ArH), 8.35 (d, $J = 7$ Hz, 2H, Pyrazole-H5); MS m/z (%) 442 (M^+, 4), 118 (17), 92 (10), 77 (100), 51 (65). Anal. calcd. for $C_{28}H_{22}N_6$ (442.53): C, 76.00; H, 5.01; N, 18.99. Found: C, 76.49; H, 5.38; N, 18.65%.

3,4-Bis[1-phenyl-1H-pyrazol-3-yl]-5-methyl-1-(4-tolyl)-1H-pyrazole (11b). Brown crystals, yield 0.77 g (78%), mp 242–244 °C; IR (KBr) ν_{max}/cm^{-1} 1596 (C=C). ^1H NMR (DMSO-d_6) δ 2.52 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.23 – 7.62 (m, 14H, ArH), 6.73 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 8.35 (d, $J = 8$ Hz, 2H, Pyrazole-H5); MS m/z (%) 459 ($M^+ + 3$, 2), 458 ($M^+ + 2$, 8), 456 (M^+, 100), 313 (12), 192 (11), 153 (12), 140 (15), 115 (15), 103 (17), 90 (38), 77 (32), 64 (17). Anal. calcd. for $C_{29}H_{24}N_6$ (456.55): C, 76.30; H, 5.30; N, 18.41. Found: C, 76.70; H, 5.70; N, 18.77%.

3,4-Bis[1-phenyl-1H-pyrazol-3-yl]-5-methyl-1-(4-anisyl)-1H-pyrazole (11c). Pale brown crystals, yield 0.80 g (85%), mp 230–232 °C; IR (KBr) ν_{max}/cm^{-1} 1599 (C=N), 1599 (C=C), 1250 (C-O-C). ^1H NMR (DMSO-d_6) δ 3.31 (s, 3H, CH_3),

3.84 (s, 3H, OCH_3), 6.82 (d, $J = 7$ Hz, 2H, Pyrazole-H4), 7.13–7.67 (m, 14H, ArH), 8.30 (d, $J = 7$ Hz, 2H, Pyrazole-H5); MS m/z (%) 474 ($M^+ + 2$, 3), 472 (M^+, 12), 167 (18), 147 (25), 140 (12), 131 (13), 118 (15), 92 (77), 76 (40), 65 (100), 50 (17). Anal. calcd. for $C_{29}H_{24}N_6O$ (472.55); C: 73.71; H, 5.12; N, 17.78. Found; C: 74.20; H, 5.47; N, 18.05%.

Synthesis of 3,4-Bis([1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-1-aryl-5-methylpyrazoles (12a–c)

3-Amino-1,2,4-triazole (0.77 g, 4 mmol), was added to a solution of **4** (0.70 g, 2 mmol) in acetic acid (20 ml). The mixture was refluxed for 6 h and then cooled. The solid that deposited after cooling was filtred and crystallized from ethanol–dioxane to give the respective product **12**.

3,4-Bis([1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-1-phenyl-5-methylpyrazole (12a). Orange solid, yield 0.60 g (77%), mp 238–240 °C; IR (KBr) ν_{max}/cm^{-1} 1617 (C=N). ^{1}H NMR (DMSO-d_6) δ 3.38 (s, 3H, CH_3), 7.65 (s, 5H, Ar-H), 7.80 (d, $J = 9$ Hz, 2H, pyrimidine-H), 8.79 (s, 2H, triazole H), 9.27 (d, $J = 9$ Hz, 2H, pyrimidine-H). MS m/z (%) 394 (M^+, 10), 83 (21), 68 (11), 56 (16), 46 (100). Anal. calcd. for $C_{20}H_{14}N_{10}$ (394.39): C, 60.91; H, 3.58; N, 35.51. Found: C, 61.15; H, 3.71; N, 35.85.

3,4-Bis([1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-1-(p-tolyl)-5-methylpyrazole (12b). Yellow solid, yield 0.61 g (75%), mp 266–268 °C; IR (KBr) ν_{max}/cm^{-1} 1609 (C=N). ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, Ar-CH_3), 3.37 (s, 3H, CH_3), 7.46 (d, $J = 9$ Hz, 2H, Ar-H), 7.58 (d, $J = 9$ Hz, 2H, Ar-H), 7.79 (d, $J = 9$ Hz, 2H, pyrimidine-H), 8.79 (s, 2H, triazole H), 9.27 (d, $J = 9$ Hz, 2H, pyrimidine-H). MS m/z (%) 408 (M^+, 12), 332 (13), 256 (30), 241 (100), 223 (11), 170 (34), 155 (19), 143 (12), 130 (40), 104 (42), 91 (57), 83 (64), 76 (22), 64 (54), 57 (34), 45 (63). Anal. calcd. for $C_{21}H_{16}N_{10}$ (408.42): C, 61.76; H, 3.95; N, 34.29. Found: C, 62.01; H, 3.84; N, 34.51%.

3,4-Bis([1,2,4]triazolo[1,5-*a*]pyrimidin-7-yl)-1-(p-anisyl)-5-methylpyrazole (12c). Pale brown solid, yield 0.67 g (80%), mp 254–256 °C; IR (KBr) ν_{max}/cm^{-1} 1687, 1617 (C=N). ^{1}H NMR (DMSO-d_6) δ 3.38 (S, 3H, CH_3), 3.84 (S, 3H, OCH_3), 7.42 (d, $J = 9$ Hz, 2H, Ar-H), 7.59 (d, $J = 9$ Hz, 2H, Ar-H), 7.79 (d, $J = 9$ Hz, 2H, pyrimidine-H), 8.79 (s, 2H, triazole H), 9.27 (d, $J = 9$ Hz, 2H, pyrimidine-H). MS m/z (%) 424 (M^+, 10), 272 (13), 257 (30), 214 (11), 223 (11), 147 (19), 121 (18), 103 (12), 91 (21), 83 (39), 68 (45), 56 (30), 45 (100). Anal. calcd. for $C_{21}H_{16}N_{10}O$ (424.42): C, 59.43; H, 3.80; N, 33.00. Found: C, 59.69; H, 3.92; N, 33.25%.

Preparation of compounds 16, 21, and 22

Malononitrile (0.26 g, 4 mmol) was added to a solution of **4** (0.70 g, 2 mmol) in glacial acetic acid in the presence of ammonium acetate (0.5 g). The reaction mixture refluxed for 25 h, and then cooled. The reaction was followed by thin-layer chromatagraphy (TLC). The reaction mixture was poured into cold water while being

stirred. The solid product that precipitated was filtered off and crystallized from ethanol to give the respective compound **16**.

When this procedure was repeated using ethyl acetoacetate and ethyl benzoyl acetate in lieu of malononitrile, the respective products **21** and **22** were produced, respectively.

3,4-Bis[5-cyano-6-oxo-1H-pyrid-2-yl]-5-methyl-1-phenyl-1H-pyrazole (16a). Orange crystals, yield 0.55 g (70%), mp 234–236 °C; IR (KBr) ν_{max}/cm^{-1} 3336 (NH), 2213 (CN), 1675 (C=O). ^{1}H NMR (DMSO-d_6) δ 3.31 (s, 3H, CH_3), 7.65 (s, 5H, ArH), 7.94 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.67 (d, $J = 9$ Hz, 2H, Pyridine-H), 13.12 (s, 2H, 2NH); MS m/z (%) 394 (M^+, 6), 328 (10), 118 (10), 91 (12), 77 (100), 66 (18), 51 (54). Anal. calcd. for $C_{22}H_{14}N_6O_2$ (394.39): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.48; H, 3.82; N, 21.44%.

3,4-Bis[5-cyano-6-oxo-1H-pyrid-2-yl]-5-methyl-1-(4-tolyl)-1H-pyrazole (16b). Yellow solid, yield 0.60 g (74%), mp 272–274 °C: IR (KBr) ν_{max}/cm^{-1} 3350 (NH), 2210 (CN), 1670 (C=O). ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3) 3.30 (s, 3H, CH_3), 7.43–7.69 (2 d, $J = 8$ Hz, 2H, ArH), 7.95 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.65 (d, $J = 9$ Hz, 2H, Pyridine-H), 12.95 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6) δ 11.3, 24.0, 100.3, 103.0, 106.2, 108.4, 115.8, 120.5, 129.7, 129.90, 136.53, 136.56, 137.0, 140.8, 156.03, 156.06, 161.5; MS m/z (%) 408 (M^+, 2), 360 (72), 342 (90), 314 (60), 298 (16), 287 (41), 258 (12), 244 (19), 216 (14), 190 (11), 177 (12), 164 (22), 155 (10), 149 (15), 127 (45), 114 (61), 103 (58), 91 (96), 76 (48), 64 (100), 50 (38). Anal. calcd. for $C_{23}H_{16}N_6O_2$ (408.41): C, 67.64; H, 3.94; N, 20.58. Found: C, 68.00; H, 4.31; N, 20.76%.

3,4-Bis[5-cyano-6-oxo-1H-pyrid-2-yl]-5-methyl-1-(4-anisyl)-1H-pyrazole (16c). Yellow crystals, yield 0.67 g (80%), mp 265–267 °C; IR (KBr) ν_{max}/cm^{-1} 3338 (NH), 2208 (CN), 1667 (C=O), 1250 (C-O-C). ^{1}H NMR (DMSO-d_6) δ 3.31 (s, 3H, CH_3) 3.85 (s, 3H, OCH_3), 7.14 (d, $J = 8$ Hz, 2H, ArH), 7.72 (d, $J = 8$ Hz, 2H, ArH), 7.94 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.59 (d, $J = 9$ Hz, 2H, Pyridine-H), 13.07 (s, 2H, 2NH); MS m/z (%) 424 (M^+, 0.6), 376 (81), 358 (100), 348 (10), 330 (56), 315 (22), 303 (47), 287 (24), 277 (10), 258 (25), 243 (16), 234 (12), 216 (23), 204 (16), 191 (25), 178 (30), 165 (30), 157 (13), 151 (32), 147 (24), 128 (49), 115 (54), 107 (69), 95 (10), 90 (75), 76 (73), 63 (59), 50 (30). Anal. calcd. for $C_{23}H_{16}N_6O_3$ (424.41): C, 65.09; H, 3.80; N, 19.80. Found: C, 65.40; H, 3.92; N, 20.22%.

3,4-Bis[5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-5-methyl-1-phenyl-1H-pyrazole (21a). Reddish crystals, yield 0.72 g (75%), mp 254 °C; IR (KBr) ν_{max}/cm^{-1} 1715 (C=O), 1582 (C=N). ^{1}H NMR (DMSO-d_6) δ 1.22 (t, $J = 7$ Hz, 6H, $2CH_3$), 2.51 (s, 6H, CH_3), 3.32 (s, 3H, CH_3), 4.27 (q, $J = 7$ Hz, 4H, 2 OCH_2), 7.61 (s, 5H, ArH), 7.95 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.69 (d, $J = 9$ Hz, 2H, Pyridine-H); MS m/z (%) 484 (M^+, 11), 483 (19), 334 (22), 280 (14), 279 (22), 254 (14), 253 (16), 236 (11), 215 (19), 194 (39), 188 (16), 163 (16), 132 (22), 118 (36), 104 (36), 91 (41), 84 (25), 79 (25), 77 (100), 70 (28), 57 (44). Anal. calcd. for $C_{28}H_{28}N_4O_4$ (484.55): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.80; H, 6.02; N, 11.88%.

3,4-Bis[5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-5-methyl-1-(4-tolyl)-1H-pyrazole (21b). Orange solid, yield 0.79 g (80%), mp. 298–300 °C, IR (KBr)

ν_{max}/cm^{-1} 1715 (C=O). ^{1}H NMR (DMSO-d_6) δ 1.22 (t, $J = 7$ Hz, 6H, $2CH_3$), 2.50 (s, 3H, Ar-CH_3), 2.72 (s, 6H, CH_3), 3.32 (s, 3H, CH_3), 4.35 (q, $J = 7$ Hz, 4H, $2OCH_2$), 7.40–7.64 (m, 4H, ArH), 7.94 (d, $J = 9$Hz, 2H, Pyridine-H), 8.71 (d, $J = 9$ Hz, 2H, Pyridine-H); MS m/z (%) 498 (M^+, 0.53), 387 (11), 289 (27), 265 (22), 193 (14), 171 (11), 165 (11), 149 (14), 141 (15), 132 (25), 122 (12), 115 (29), 105 (51), 97 (28), 91 (87), 81 (22), 76 (52), 69 (42), 63 (80), 56 (45), 45 (100). Anal. calcd. for $C_{29}H_{30}N_4O_4$ (498.57): C, 69.86; H, 6.06; N, 11.24. Found: C, 70.20; H, 6.40; N, 11.53%.

3,4-Bis[5-ethoxycarbonyl-6-methyl-pyrid-2-yl]-5-methyl-1-(4-anisyl)-1H-pyrazole (21c). Pale brown crystals, yield 0.88 g (86%), mp 280–282 °C; IR (KBr) ν_{max}/cm^{-1} 1720 (C=O), 1250 (C-O-C). ^{1}H NMR (DMSO-d_6) δ 1.07 (t, $J = 7$ Hz, 6H, $2CH_3$), 2.49 (s, 6H, $2CH_3$), 3.31 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.25 (q, $J = 7$ Hz, 4H, $2OCH_2$), 7.13–7.56 (m, 4H, ArH), 7.95 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.70 (d, $J = 9$ Hz, 2H, Pyridine-H); ^{13}C NMR (DMSO-d_6) δ 11.4, 12.8, 18.0, 55.9, 60.3, 107.6, 114.2, 115.0, 119.3, 120.46, 120.50, 120.53, 120.56, 129.3, 132.0, 136.0, 137.8, 147.7, 156.03, 156.06, 158.2, 162.0, 166.5; MS m/z (%) 514 (M^+, 0.50), 375 (11), 334 (58), 306 (40), 281 (36), 278 (14), 179 (12), 165 (22), 157 (10), 148 (39), 138 (14), 131 (15), 122 (42), 115 (22), 103 (69), 91 (90), 76 (99), 63 (100), 54 (63), 50 (77). Anal. calcd. for $C_{29}H_{30}N_4O_5$ (514.57): C, 67.69; H, 5.88; N, 10.89. Found: C, 67.25; H, 6.20; N, 11.12%.

3,4-Bis[5-ethoxycarbonyl-6-phenyl-pyrid-2-yl]-5-methyl-1-phenyl-1H-pyrazole (22a). Yellow solid, yield 0.96 g (79%), mp 232–234 °C; IR (KBr) ν_{max}/cm^{-1} 1710 (C=O). ^{1}H NMR (DMSO-d_6) δ 1.22 (t, $J = 7$ Hz, 6H, $2CH_3$), 3.52 (s, 3H, CH_3), 4.29 (q, $J = 7$ Hz, 2H, 2 OCH_2), 7.58 (s, 15H, ArH), 7.98 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.28 (d, $J = 9$Hz, 2H, Pyridine-H); MS m/z (%) 608 (M^+, 17), 527 (12), 347 (44), 335 (12), 214 (47), 187 (44), 185 (12), 176 (17), 160 (29), 145 (18), 144 (18), 132 (32), 118 (35), 104 (32), 91 (38), 78 (44), 77 (82), 69 (32), 65 (64), 60 (47), 51 (100). Anal. calcd. for $C_{38}H_{32}N_4O_4$ (608.69): C, 74.98; H, 5.30; N, 9.20. Found: C, 75.33; H, 5.40; N, 9.56%.

3,4-Bis[5-ethoxycarbonyl-6-phenylpyrid-2-yl]-5-methyl-1-(4-tolyl)-1h-pyrazole (22b). Yellow crystals, yield 0.95 g (77%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} 1710 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.22 (t, $J = 7$ Hz, 6H, $2CH_3$), 2.41 (s, 3H, Ar-CH_3), 3.31 (s, 3H, CH_3), 4.25 (q, $J = 7$ Hz, 4H, 2 OCH_2), 7.43–7.51 (m, 14 H, ArH), 7.94 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.24 (d, $J = 9$ Hz, 2H, Pyridine-H); MS m/z (%) 623 ($M^+ + 1$, 0.08), 622 (M^+, 0.08), 376 (17), 347 (19), 317 (23), 288 (23), 272 (11), 236 (12), 229 (18), 220 (26), 183 (15), 178 (14), 165 (22), 153 (31), 141 (46), 131 (36), 120 (19), 115 (52), 103 (90), 89 (80), 76 (97), 63 (100). Anal. calcd. for $C_{39}H_{34}N_4O_4$ (622.71): C, 75.22; H, 5.50; N, 9.00. Found: C, 75.33; H, 5.78; N, 9.40%.

3,4-Bis[5-ethoxycarbonyl-6-phenylpyrid-2-yl]-5-methyl-1-(4-anisyl)-1H-pyrazole (22c). Pale brown solid, yield 0.99 g (78%), mp 282–284 °C, IR (KBr) ν_{max}/cm^{-1} 1710 (C=O), 1251 (C-O-C). ^{1}H NMR (DMSO-d_6) δ 1.22 (t, $J = 7$ Hz, 6H, $2CH_3$), 3.3 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.28 (q, $J = 7$ Hz, 4H, $2OCH_2$), 7.13–7.56 (s, 14H, ArH), 7.93 (d, $J = 9$ Hz, 2H, Pyridine-H), 8.35 (d, $J = 9$ Hz, 2H, Pyridine-H); ^{13}C NMR (DMSO-d_6) δ 11.3, 12.8, 55.9, 60.3, 107.7, 114.6, 119.3,

120.5, 127.53, 127.56, 132.0, 135.0, 138.8, 147.7, 156.03, 156.06, 158.2, 166.3; MS m/z (%) 638 (M^+, 0.5), 148 (12), 104 (22), 90 (61), 76 (78), 62 (100). Anal. calcd. for $C_{39}H_{34}N_4O_5$ (638.71): C, 73.34; H, 5.37; N, 8.77. Found: C, 73.68; H, 5.16; N, 8.98%.

Alternate Synthesis of 16b

Cyanoacetamide (0.33 g, 4 mmol) was added to a solution of **4b** (0.73 g, 2 mmole) in dry toluene, and the mixture was refluxed for 12 h and then cooled. The solid so formed was filtered off and crystallized from ethanol to give compound **16b** (0.61 g, 85%), mp 272–274 °C, which proved identical in all respects (mp, mixed mp, and spectral data) with **16b**.

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