Reaction of Hydrazonoyl Halides with *Bis*-enaminones: A Convenient Route for Synthesis of Novel Polyaza-Terheterocycles

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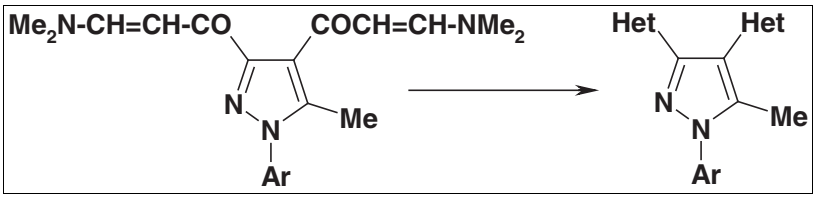

New *bis*(pyrazolylenaminones) were prepared in good yields. Their synthetic utilities as precursors for regioselective synthesis of novel *bis*(hetarylpyrazoles) were also investigated. The mechanisms and selectivities observed in the studied reactions were discussed.

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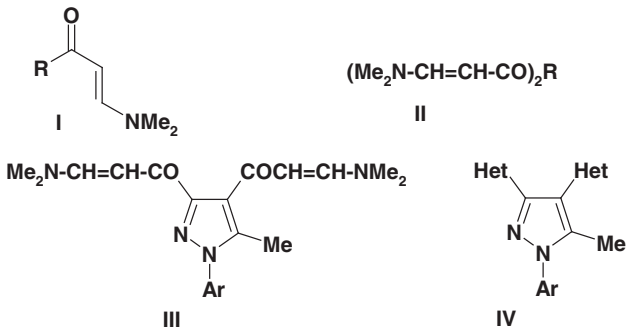
INTRODUCTION

Over the past 30 years, we have been interested in the chemistry of hydrazonoyl halides [RC(X)═NNHAr]. At present, there are several review articles by Shawali *et al*. [1–12] covering their synthesis, physical properties, chemical reactions, and applications. In addition, the chemistry of enaminones of the general formula **I** (Chart 1) has been extensively investigated by many research groups all over the world because of their utility as versatile precursors for synthesis of heterocyclic compounds of various pharmaceutical properties [13–21]. Furthermore, *bis*-enaminones of the general formula **II** (Chart 1) have been shown in some reports to be useful precursors for synthesis of some *bis*-heterocycles [22–27]. In the light of these findings and in connection with our ongoing studies of the chemistry of hydrazonoyl halides [1–12], it was thought interesting to explore the synthesis and reactions of the new *bis*(enaminones), namely 3,4-*bis*[(*N*,*N*′-dimethylamino)-1-oxo-propen-en-1-yl]-1-aryl-5-methyl-pyrazoles **III** and study their reactions with hydrazonoyl halides (Chart 1). Our interest after such a study is to develop a new one-step synthetic strategy for 3,4-dihetarylpyrazoles of the general formula **IV** (Chart 1). This is because many pyrazole derivatives and ter-pyrazole derivatives exhibit various medicinal and pharmaceutical applications [28–30].

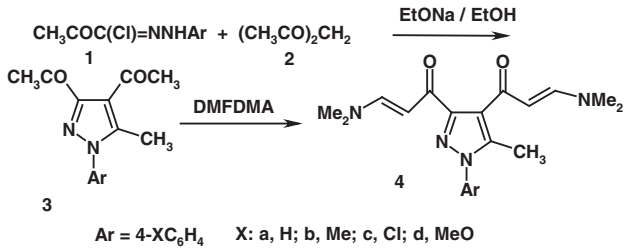
RESULTS AND DISCUSSION

The required 1-aryl-3,4-diacetyl-5-methylpyrazoles **3** precursors for synthesis of the new *bis*-enaminones **3** were prepared in this study by reaction of 2,4-pentanedione **2** with each of N-aryl 2-oxopropanehydrazonoyl chlorides **1a–d** in ethanol in the presence of sodium ethoxide (Scheme 1). The structures of the latter diacetylpyrazoles **3a–c** were confirmed by their elemental analyses and spectral data (Experimental). For example, their IR spectra revealed C═O absorption bands in the region υ 1675–1696 cm^{-1}. Their ^1H NMR spectra, in addition to the expected signals due to the aromatic protons (Experimental), exhibit singlet signals near δ 2.56 (s, 6H) and 3.30 (s, 3H) assignable to the two acetyl and the 5-methyl groups, respectively. Reaction of each of compounds **3a–c** with dimethylformamide–dimethylacetal (DMF–DMA) under reflux afforded the respective *bis*-enaminones **4a–c** (Scheme 1). The structures of the latter *bis*-enaminones **4** were confirmed by their spectra and elemental analyses. For example, their IR spectra showed C═O bands in the region υ 1635–1650 cm^{-1}. In addition to the signals of the aromatic protons, their ^1H NMR spectra revealed a singlet signal due to 5-CH_3 in the region δ 3.30–3.41 and two singlet signals at δ 2.81–2.83 (6H) and 3.07–3.08 (6H) for the protons of the two –N$(CH_3)_2$ groups. Also, such spectra showed in each case, two characteristic doublet signals at δ 5.25–5.27 (d, 2H) and 7.30–7.37 (d, 2H) with coupling constant $J = 13$ Hz assignable to the two olefinic protons. This coupling constant value indicates that the *bis*-enaminones **4** have the indicated E-configuration (Scheme 1).

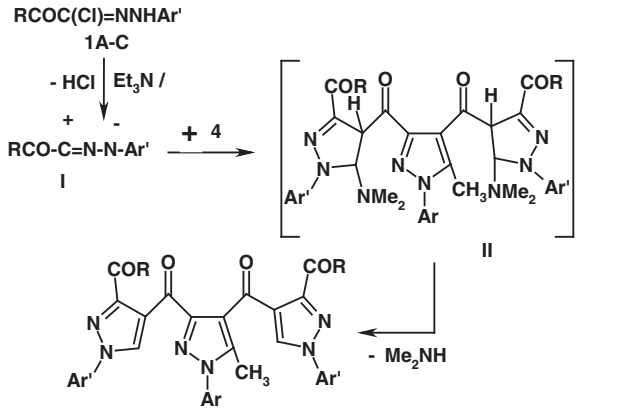
The reactions of the *bis*-enaminones **4** as dipolarophiles, with nitrilimines **I**, generated *in situ* by base-catalyzed dehydrochlorination of the respective hydrazonoyl chlorides **1A–C**, were next examined (Scheme 2). Thus, in our hands, reaction of each of **4a–d** with hydrazonoyl chlorides **1A–C** in refluxing benzene in the presence of triethylamine yielded, in each case, a single product. The isolated products were identified, on the basis of their elemental analyses and spectral (IR, ^1H NMR and MS) data (Experimental), as the respective 3,5-*Bis*-(1-phenyl-3-substituted-pyrazol-4-carbonyl)-5-methyl-1-aryl-pyrazoles **5–7** (Scheme 2). For example, the 1H NMR spectra of the products isolated



Scheme 1



Scheme 2



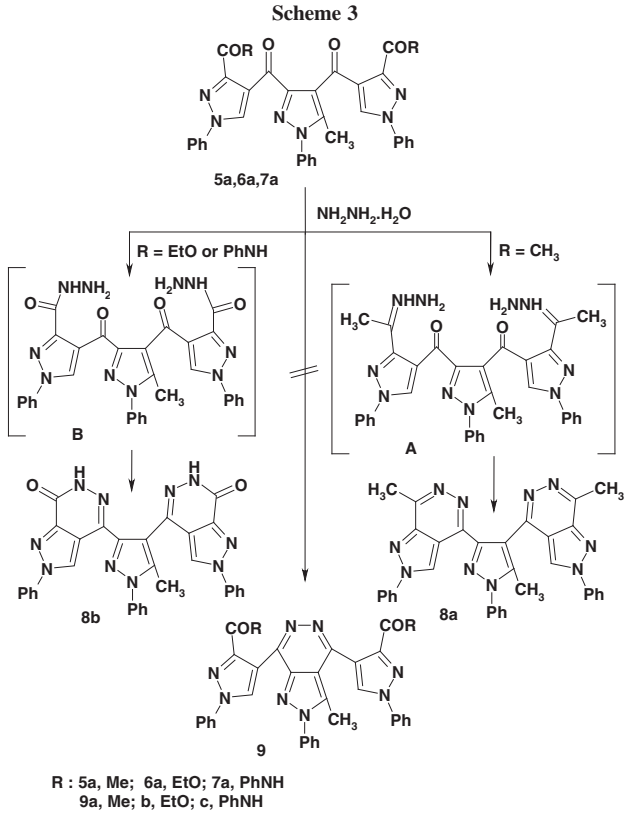
	R		X / Y		X / Y
1A (5)	Me	a	H / H	d	4-MeO / H
1B (6)	EtO	b	4-Me / H	e	H / 4-Me
1C (7)	PhNH	c	4-Cl / H	f	H / 4-Cl

showed in each case two singlet signals (1H each) in the region d 7.73–7.93 and 8.58–9.22, which correspond to the two distinct H-5 protons of the two pyrazole ring residues in such products. To account for the formation of such products, it is suggested, as depicted in Scheme 2, that the reaction of **4** with each of **1A–C** proceeds via initial 1,3-dipolar cycloaddition of nitrilimine, derived from **1**, to the activated double bonds in the *bis*-enaminone **4** to afford the non-isolable cycloadducts **II** as intermediates that undergo *in situ* elimination of dimethylamine to give **5–7** as end products. This suggested pathway is consistent with literature reports that indicate the reaction of hydrazonoyl halides with various enaminones is regioselective and lead to the formation of 5 unsubstituted pyrazole derivatives [10,17,18].

The products **5–7** were obtained in overall good yields 75–84% (Experimental). The data show that an electron-withdrawing group such as Cl group in the hydrazonoyl chloride **1** increases the yield of the products **6** and **7**. However, such a group was found to decrease the yield of the product **5** whether it is present in the bis-enaminone **4** or the hydrazonoyl chloride **1**.

Next, the reaction of **5–7** with hydrazine hydrate was examined to shed some light on its site selectivity as such hydrazinolysis can lead to the pyrazolopyridazines **8** and/or **9** (Scheme 3). In our hands, when a mixture of **5a** and hydrazine hydrate was refluxed, it yielded only one product as evidenced by TLC of the crude product. The IR spectrum of the isolated product showed the absence of carbonyl absorption bands. On the basis of this finding and other spectral data (Experimental), the isolated product was assigned structure **8a** (Scheme 3). This finding indicates that the studied reaction of hydrazine hydrate with **5a** is site-selective. To provide further evidence for this site-selectivity,

Scheme 3



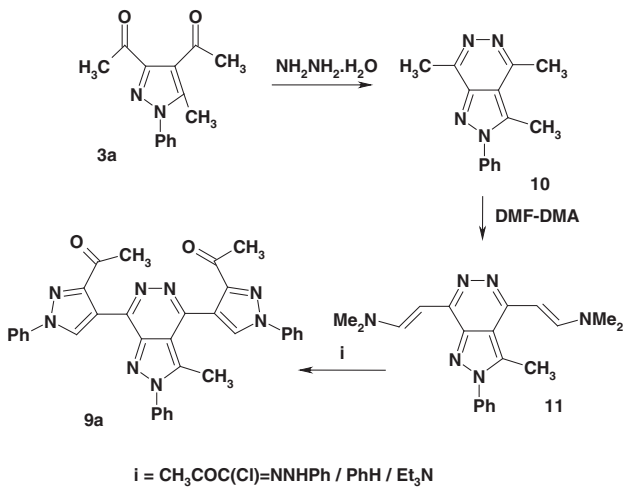
the reactions of hydrazine hydrate with both **6a** and **7a** were carried out. The studied reactions afforded, in both cases, one and the same product, whose spectra (IR, ^{1}H NMR, and MS) and elemental analysis data proved it to have structure **8b** (Scheme 3). To account for the observed site selectivity, it is suggested that hydrazine hydrate attacks first the pendant carbonyl groups (CH_3CO, EtOCO, and PhNHCO) because they are least hindered to form the corresponding intermediates of type **A** and **B**, which in turn undergo dehydrative cyclization to form the respective product **8**. This automatically nullifies the possibility of formation of the other isomers of type **9** (Scheme 3).

An unambiguous evidence for the observed site selectivity in the foregoing reaction of hydrazine hydrate with each of **5**,**6**, and **7** was provided by comparison of the product **8a** with a sample of **9a** prepared by independent synthesis as depicted in Scheme 4. Thus, reaction of pyrazole derivative **3a** with hydrazine hydrate yielded the respective pyrazolo [3,4-*d*]pyridazine derivative **10**. Heating the latter with DMF–DMA afforded the *bis*-enamine **11**. The structures of both **10** and **11** were compatible with their spectra (IR, ^{1}H NMR, and Ms) and elemental analyses (Experimental). Reaction of the latter *bis*-enamine **11** with hydrazonoyl chloride **1a** in benzene in the presence of triethylamine yielded **9a** as end product. The latter was found to have different physical properties (mp, IR, ^{1}H NMR, and Ms) and elemental analysis from that of **8a** (Experimental).

CONCLUSION

In summary, the studied reactions of hydrazonoyl halides with each of the *bis*-enaminones **4a–d** and *bis*-enamine **11** proved useful for synthesis of novel terheterocycles. The mechanism and selectivity of the studied reactions were discussed.

Scheme 4



EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr using Pye Unicam SP-1000 spectrophotometer (Pye Unicam Ltd., Cambridge, UK). ^{1}H NMR spectra were recorded in $DCCl_3$ and DMSO-d_6 using a Varian Em-200 MHz spectrometer (Varian, Santa Clara, CA) and TMS as internal reference. Mass spectra were recorded on AEI MS 30 mass spectrometer operating at 70 eV (Shimadzu Scientific Intruments, Tokyo, Japan). Elemental analyses were carried out at the Microanalytical Centre of Cairo University. The hydrazonoyl halides **1A–C** were prepared following literature procedures [31–34].

Preparation of 3,4-Diacetyl-5-methyl-1-aryl-1*H*-pyrazoles (3a–d). General method: To sodium ethoxide solution, prepared from sodium metal (0.46 g, 0.02 g atom) and absolute ethanol (15 mL), was added 2,4-pentanedione **2** (2 g, 0.02 mol). The mixture was stirred for 10 min. To the resulting solution was added the appropriate hydrazonoyl chloride **1** (0.02 mol), and the reaction mixture was left overnight at room temperature while being stirred. The solid, which precipitated, was filtered off, washed with water, dried, and finally crystallized from appropriate solvent to give the respective **3**. The compounds **3a–d** prepared together with their physical constants are listed in the succeeding text.

3,4-Diacetyl-5-methyl-1-phenyl-1H-pyrazole (3a). White crystals, (0.18 g, 77% yield), mp 132°C (EtOH) (Lit. mp 130°C [35]); IR (KBr) ν_{max}/cm^{-1} 1684 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 6H, $2COCH_3$), 3.31 (s, 3H, CH_3), 7.55–7.59 (m, 5H, Ar–H); MS *m/z* (%): 242 (M^+, 8), 227 (100), 185 (16), 156 (15), 141 (7), 128 (8), 117 (24), 77 (39). *Anal*. Calcd for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.11; H, 6.10; N, 11.46%.

3,4-Diacetyl-5-methyl-1(4-methylphenyl)-1H-pyrazole (3b). White crystals, (0.17 g, 70% yield), mp 96–98°C (EtOH) (Lit. mp 90°C [36]); IR (KBr) ν_{max}/cm^{-1} 1686 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 2.57 (s, 6H, $2COCH_3$), 3.30 (s, 3H, CH_3), 7.37 (d, J = 8 Hz, 2H, Ar–H), 7.44 (d, J = 8 Hz, 2H, Ar–H); MS *m/z* (%): 256 (M^+, 46), 241 (100), 198 (20), 170 (16), 155 (12), 131 (25), 122 (11), 90 (41), 76 (8). *Anal*. Calcd for $C_{15}H_{16}N_2O_2$ (256.31): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.31; H, 6.44; N, 10.88%.

3,4-Diacetyl-5-methyl-1(4-chlorophenyl)-1H-pyrazole (3c). White crystals, (0.19 g, 70% yield), mp 152°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1696, 1675 (C=O); ^{1}H NMR (DMSO, d_6): δ 2.57 (s, 6H, $2COCH_3$), 3.28 (s, 3H, CH_3), 7.66–7.67 (m, 4H, Ar–H); MS *m/z* (%): 278 (M^+ + 2, 19), 276 (M^+, 46), 261 (100), 219(12), 152(28), 122 (18), 110 (39), 77 (20). *Anal* Calcd for $C_{14}H_{13}ClN_2O_2$ (276.72): C, 60.77; H, 4.74; N, 10.12. Found: C, 60.70; H, 4.80; N, 10.14%.

3,4-Diacetyl-5-methyl-1(4-methoxyylphenyl)-1H-pyrazole (3d). White crystals, (0.16 g, 60% yield), mp 126°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1682 (C=O), 1255 (C–O–C); ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 6H, $2COCH_3$), 3.26 (s, 3H, CH_3), 3.89 (s, 3H,OCH_3), 7.12 (d, J = 8 Hz, 2H, Ar–H), 7.45 (d, J = 8 Hz, 2H, Ar–H); MS *m/z* (%): 272 (M^+, 59), 257 (100), 213 (25), 199 (11), 172 (17), 158 (16), 147 (31), 127 (12), 108 (16), 94 (21), 76 (20). *Anal*. Calcd for $C_{15}H_{16}N_2O_3$ (272.31): C, 66.16; H, 5.92; N, 10.29. Found: C, 65.89; H, 6.25; N, 10.13%.

Synthesis of 3,4-Bis[3-(*N*,*N*-dimethylamino)acryloyl]-1-aryl-5-methyl-1*H*-pyrazoles (4a–d). General method: A mixture of appropriate pyrazole derivative **3** (10 mmol) and DMF–DMA (2.5 g, 20 mmol) was refluxed for 20–30 h 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 *bis*-enaminone **4**. The compounds **4a–d** together with their physical constants are listed in the succeeding text.

3,4-Bis[3-(N,N-dimethylamino)acryloyl]-1-phenyl-5-methyl-1H-pyrazole (4a). Pale brown solid, (0.31 g, 88% yield), mp 148–150°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1642 (C═O); ^1H NMR (DMSO-d_6): δ 2.83 (s, 6H, $N(CH_3)_2$), 3.08 (s, 6H, $N(CH_3)_2$), 3.40 (s, 3H, CH_3), 5.30 (d, J = 13 Hz, 2H, ═CH), 5.60 (d, J = 13 Hz, 2H, ═CH), 7.32–7.57 (m, 5H, Ar–H); MS *m/z* (%): 353 (M^+ + 1, 5), 352 (M^+, 22), 334 (13), 317 (15) 308 (41) , 290 (12), 282 (31), 280 (14), 264 (20), 118 (18), 98 (100), 82 (18), 77 (33). *Anal.* Calcd for $C_{20}H_{24}N_4O_2$ (352.44): C, 68.16; H, 6.86; N, 15.90. Found: C, 67.94; H, 6.89; N, 15.76%.

3,4-Bis[3-(N,N-dimethylamino)acryloyl]-1-(p-tolyl)-5-methyl-1H-pyrazole (4b). Pale yellow solid, (0.31 g, 84% yield), mp 134°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1643 (C═O); ^1H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 2.83 (s, 6H, $N(CH_3)_2$), 3.07 (s, 6H, $N(CH_3)_2$), 3.39 (s, 3H, CH_3), 5.29 (d, J = 13 Hz, 2H, ═CH), 5.60 (d, J = 13 Hz, 2H, ═CH), 7.37–7.59 (m, 4H, ArH); MS *m/z* (%): 368 (M^+ + 2, 0.4), 367 (M^+ + 1, 2), 366 (M^+, 8), 322 (15) 296 (14), 132 (16), 98 (100), 91 (18), 82 (17), 71 (15). *Anal.* Calcd for $C_{21}H_{26}N_4O_2$ (366.47): C, 68.83; H, 7.15; N, 15.29. Found: C, 68.90; H, 7.40; N, 15.28%.

3,4-Bis[3-(N,N-dimethylamino)acryloyl]-1-(p-chlorophenyl)-5-methyl-1H-pyrazole (4c). Brown solid, (0.32 g, 83% yield), mp 160°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1648, 1635 (C═O); ^1H NMR (DMSO-d_6): δ 2.81(s, 6H, $N(CH_3)_2$), 3.08 (s, 6H, $N(CH_3)_2$), 3.30 (s, 3H, CH_3), 5.25 (d, 2H, J = 13 Hz, ═CH), 7.31 (d, J = 13 Hz, 2H, ═CH), 7.54–7.61(2d, J = 8 Hz, 4H, Ar–H); MS *m/z* (%): 388 (M^+ + 2, 3), 386 (M^+ + , 7), 369 (14), 351 (12), 342 (22), 316 (17), 298(15), 258 (7), 151(18), 110 (15), 98 (100), 81 (17), 77 (3). *Anal*. Calcd for $C_{20}H_{23}ClN_4O_2$ (386.88): C, 62.09; H, 5.99; N, 14.48. Found: C, 62.11; H, 6.02; N, 14.50%.

3,4-Bis[3-(N,N-dimethylamino)acryloyl]-1-(p-methoxyphenyl)-5-methyl-1H-pyrazole (4d). Brown solid, (0.32 g, 84% yield), mp 144°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1643 (C═O); ^1H NMR (DMSO-d_6): δ 2.82 (s, 6 H, $N(CH_3)_2$), 3.07 (s, 6H, $N(CH_3)_2$), 3.41 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3) 5.26 (d, J = 13 Hz ,2H, ═CH), 5.59 (d, J = 13 Hz, 2H, ═CH), 7.15 (d, J = 7 Hz, 2H, ArH), 7.6 (d, J = 7 Hz, 2H, ArH); MS *m/z* (%): 383 (M^+ + 1, 2), 382 (M^+, 4), 338 (12), 294 (11) 148 (16), 98 (100), 82 (14), 77 (16). *Anal*. Calcd for $C_{21}H_{26}N_4O_3$ (382.47): C, 65.95; H, 6.85; N, 14.65. Found: C, 65.57; H, 7.21; N, 14.54%.

Reaction of bis-enaminones with hydrazonoyl chlorides. General procedure: To a stirred solution of the appropriate *bis*-enaminone **4** (1 mmol) and the hydrazonoyl chloride **1** (2 mmol) in dry benzene (30 mL), triethylamine (0.5 mL) was added and the mixture was refluxed for 15–20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with methanol. The solid product, so formed in each case, was filtered off, washed with water, dried, and crystallized from ethanol to afford the corresponding pyrazole derivative. The compounds **5–7** prepared are listed in the succeeding text together with their physical constants.

3,4-Bis-(1-phenyl-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (5a). Red solid, (0.49 g, 84% yield), mp 110–112°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1689, 1642 (C═O); ^1H NMR (DMSO-d_6): δ 2.57 (s, 6H, $2COCH_3$), 2.79 (s, 3H, CH_3), 7.35–7.59 (m, 15,Ar–H), 7.85 (s, 1H, pyrazole-H-5), 9.33 (s, 1H, pyrazole-H-5); MS *m/z* (%): 583 (M^+ + 1, 1), 424 (14), 384 (10), 371 (22), 355 (39), 340 (10), 254 (28), 213 (47), 184 (17), 142 (13), 129 (12) , 117 (54), 98 (30), 91(30), 85 (95), 77(57), 45 (100). *Anal*. Calcd for $C_{34}H_{26}N_6O_4$ (582.62): C, 70.09; H, 4.50; N, 14.42, Found: C, 70.39; H, 4.75; N, 14.51%.

3,4-Bis-(1-phenyl-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1-p-tolyl-pyrazole (5b). Pale red solid, (0.48 g, 80% yield), mp 98°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1693, 1642 (C═O); ^1H NMR (DMSO-d_6): δ 2.33 (s, 6H, $ArCH_3$), 2.68 (s, 6H, $2COCH_3$), 2.80 (s, 3H, CH_3), 7.13–7.35 (m, 13H, ArH), 7.83 (s, 1H, pyrazole-H-5), 8.60 (s, 1H, pyrazole-H-5); MS *m/z* (%): 598 (M^+ + 2, 4), 597(M^+, 14), 553(47), 531(14), 514 (16), 481 (19), 464 (17), 448 (13), 438 (30), 398 (22), 390 (15), 384 (17), 370 (30), 268 (54), 254 (78), 249 (19), 213 (100), 185 (13), 170 (20), 138 (19), 132 (28), 118 (32), 104 (23), 98 (82), 90 (44). *Anal.* Calcd for $C_{35}H_{28}N_6O_4$ (596.65): C, 70.46; H, 4.73; N, 14.09. Found: C, 70.70; H, 4.80; N, 14.30%.

3,4-Bis-(1-phenyl-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1 (4-chloro-phenyl)-pyrazole (5c). Deep brown solid, (0.48 g, 77% yield), mp 122–124°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1689, 1642 (C═O); ^1H NMR (DMSO-d_6): δ 2.67 (s, 6H, $2COCH_3$), 2.78 (s, 3H, CH_3), 7.01–7.89 (m, 14H, ArH), 7.84 (s, 1H, pyrazole-H-5), 8.58 (s, 1H, pyrazole-H-5); MS *m/z* (%): 619 (M^+ + 2, 2), 617 (M^+, 3), 574 (15), 502 (17), 458 (42), 389(28), 296 (12), 288 (60), 270 (19), 213 (100), 170 (23), 151 (37), 117 (26), 103 (27), 97 (67), 77(32). *Anal.* Calcd for $C_{34}H_{25}ClN_6O_4$ (617.07): C, 66.18; H, 4.08; N, 13.62. Found: C, 66.45; H, 4.20; N, 13.85%.

3,4-Bis-(1-phenyl-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1-(p-methoxyphenyl)-pyrazole (5d). Brown solid, (0.48 g, 78% yield), mp 92°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1693, 1643 (C═O); ^1H NMR (DMSO-d_6): δ 2.68 (s, 6H, $2COCH_3$), 2.82 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.07–7.96 (m, 14H, Ar–H), 7.80 (s, 1H, pyrazole-H-5), 8.60 (s, 1H, pyrazole-H-5); MS *m/z* (%): 612 (M^+, 3), 284 (11), 213 (26), 148 (16), 142 (10), 103 (10), 98 (48), 92 (17), 77 (100). *Anal.* Calcd for $C_{35}H_{28}N_6O_5$ (612.65): C, 68.62; H, 4.61; N, 13.72. Found: C, 68.82; H, 4.79; N, 13.95%.

3,4-Bis-(1-(p-tolyl)-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (5e). Orange solid, (0.48 g, 79% yield), mp 136–138°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1676, 1644 (C═O); ^1H NMR (DMSO-d_6): δ 2.26 (s, 6H, 2Ar-CH3), 2.49 (s, 6H, $COCH_3$), 2.90 (s, 3H, CH_3), 7.13–7.35 (m, 13H, ArH), 7.87 (s, 1H, pyrazole-H-5), 8.61 (s, 1H, pyrazole-H-5); MS *m/z* (%): 611 (M^+ + 1, 2), 368 (18), 254 (26), 227 (27), 209 (23), 185 (11), 154 (12.73), 131 (30), 125 (12), 122 (17), 117 (34), 105 (71), 97 (61), 90 (28), 82 (52), 77 (38), 70(100). *Anal.* Calcd for $C_{36}H_{30}N_6O_4$ (610.23): C, 70.81; H, 4.95; N, 13.76. Found: C, 70.86; H, 4.96; N, 13.79%.

3,4-Bis-(1-(p-chlorophenyl)-3-acetyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (5f). Brown solid, (0.50 g, 77% yield), mp 160°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1683, 1640 (C═O); ^1H NMR (DMSO-d_6): δ 2.48 (s, 6H, 2 $COCH_3$), 3.10 (s, 3H, CH_3), 7.38 (d, J = 8 Hz ,4H), 7.44 (d, J = 8.4 Hz, 4H), 7.2–7.7 (m, 5H, ArH), 7.84 (s, 1H, Pyrazole-H-5), 8.55 (s, 1H, Pyrazole-H-5); MS *m/z* (%): 652 (M^+ + 1, 6), 609 (22), 390 (10), 387 (10), 254 (15), 247 (32), 232 (25), 230 (35), 154 (20), 152 (54), 139 (20), 125 (100), 118 (20), 110 (30) , 98 (70), 90 (32), 82(29), 77 (23). *Anal.* Calcd for $C_{34}H_{24}Cl_2N_6O_4$ (651.50): C, 62.68; H, 3.71; N, 12.9. Found: C, 62.70; H, 3.75; N, 13.03%.

3,4-Bis-(1-phenyl-3-ethoxycarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (6a). Orange solid, (0.3 g, 47% yield), mp 80°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1700, 1640 (C═O); ^1H NMR (DMSO-d_6): δ 1.29 (t, J = 7 Hz, 6H, $2CH_3$), 3.33 (s, 3H, CH_3), 4.28 (q, J = 7 Hz, 4H, $2CH_2$), 7.14–7.70 (m,

15H, Ar–H), 7.95 (s, 1H, pyrazole-H-5), 9.22 (s, 1H, pyrazole-H-5); MS *m/z* (%): 644.85 ($M^+ + 2$, 0.64), 643.10 ($M^+ + 1$, 4), 570 (15), 498 (12), 480 (15), 424 (11), 407 (13), 355 (30), 340 (17), 325 (12), 264 (13), 255 (20), 244 (27), 237 (14), 224 (17), 215 (33), 210 (20), 184 (17), 171 (20), 154 (15), 128 (18), 118 (84), 104 (55), 98 (57), 92 (80), 81 (12), 77 (100). *Anal*. Calcd for $C_{36}H_{30}N_6O_6$ (642.68): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.58; H, 4.80; N, 13.12%.

3,4-Bis-(1-(p-tolyl)-3-ethoxycarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (6e). Yellow crystal, (0.50 g, 75% yield), mp 100°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1708, 1640 (C═O); ^{1}H NMR (DMSO-d_6): δ 1.31 (t, *J* = 7 Hz, 6H, $2CH_3$), 2.24 (s, 6H, CH_3), 3.32 (s, 3H, CH_3), 4.29 (q, *J* = 7 Hz, 4H, $2CH_2$), 7.11–7.26 (m, 13H, Ar–H) , 7.84 (s, 1H, pyrazole-H-5), 8.60 (s, 1H, pyrazole-H-5); MS *m/z* (%): 671 ($M^+ + 1$, 59), 242 (11), 241 (25), 166 (17), 132 (10), 118 (12), 104 (100), 90 (15), 77 (34). *Anal*. Calcd for $C_{38}H_{34}N_6O_6$ (670.73): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.10; H, 5.18; N, 12.60%.

3,4-Bis-(1-(p-4-chlorophenyl)-3-ethoxycarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (6f). Yellow crystal, (0.55 g, 77% yield), mp 146–148°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 1710, 1640 (C═O); ^{1}H NMR (DMSO-d_6): δ 1.31 (t, *J* = 7 Hz, 6H, $2CH_3$), 3.30 (s, 3H, CH_3), 4.30 (q, *J* = 7 Hz, 4H, $2CH_2$), 7.36–7.56 (m,13H, Ar–H), 7.90 (s, 1H, Pyrazole-H-5), 8.58 (s, 1H, Pyrazole-H-5); MS *m/z* (%): 711.85 (M^+, .11), 262 (18), 260 (24), 254 (26), 188 (16), 186 (28), 138 (11), 125 (100), 118 (21), 110 (17), 98 (73), 80 (29), 77(19). *Anal*. Calcd for $C_{36}H_{28}Cl_2N_6O_6$ (711.57): C, 60.77; H, 3.97; N, 11.81. Found: C, 60.80; H, 4.00; N, 11.85%.

3,4-Bis-(1-phenyl)-3-phenylaminocarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (7a). Brown solid, (0.58 g, 79% yield), mp 160°C (EtOH/Dioxane); IR (KBr) ν_{max}/cm^{-1} 3390 (NH), 1682, 1643 (C═O); ^{1}H NMR (DMSO-d_6): δ 3.31 (s, 3H, CH_3), 7.05–7.66 (m, 25H, Ar–H), 7.89 (s, 1H, pyrazole-H-5), 9.20 (s, 1H, pyrazole-H-5), 9.95 (s, 2H, 2NH); MS *m/z* (%): 738.05 ($M^+ + 2$, 12), 355 (20), 237 (10), 144 (12), 133 (11) , 118 (76), 104 (26), 92 (100), 76 (72). *Anal*. Calcd for $C_{44}H_{32}N_8O_4$ (736.80): C, 71.73; H, 4.38; N, 15.21. Found: C,71.82; H,4.42; N,15.23%.

3,4-Bis-(1-p-tolyl)-3-phenylaminocarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (7e). Deep orange solid, (0.60 g, 78% yield), mp 166–168°C (EtOH/Dioxane); IR (KBr) ν_{max}/cm^{-1} 3382 (NH), 1683, 1644 (C═O); ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 6H, $ArCH_3$), 3.31 (s, 3H, CH_3), 7.09–7.72 (m, 23H, Ar–H), 7.89(s, 1H, Pyrazole-5-H), 8.60 (s, 1H, Pyrazole-5-H), 9.84 (s, 2H, 2NH); MS *m/z* (%): 766 ($M^+ + 2$, .29), 765 ($M^+ + 1$, 0.34), 618 (12), 526 (19), 304 (20), 412 (12), 255 (62), 238 (26), 185 (24), 370 (56), 155 (14), 152 (11), 149 (11), 140 (28), 130 (25), 118 (81), 109 (12), 105 (71), 98 (100), 93 (44), 77 (75). *Anal*. Calcd for $C_{46}H_{36}N_8O_4$ (764.85): C, 72.24; H, 4.74; N, 14.65. Found: C, 72.26; H, 4.74; N, 14.75%.

3,4-Bis-(1-(p-chlorophenyl)-3-phenylaminocarbonyl-pyrazol-4-carbonyl)-5-methyl-1-phenyl-pyrazole (7f). Pale red solid, (0.68 g, 81% yield), mp 180°C (EtOH); IR (KBr) ν_{max}/cm^{-1} 3387(NH), 1680, 1640 (C═O); ^{1}H NMR ($CDCl_3$): δ 3.17 (s, 3H, CH_3), 7.12–7.53 (m, 23H, Ar–H), 7.73 (s, 1H, Pyrazole-H-5), 8.58 (s, 1H, Pyrazole-H-5), 10.05 (s, 2H, 2 NH); MS *m/z* (%): 806 ($M^+ + 2$, 0.4), 254 (37), 390 (15), 238 (18), 152 (10), 138 (12), 126 (15), 118 (48), 104 (15) , 98 (61), 92 (60), 77 (52), 70 (42), 45 (100). *Anal*. Calcd for $C_{44}H_{30}Cl_2N_8O_4$ (805.69): C, 65.60; H, 3.75; N, 13.91. Found: C, 65.90; H, 4.00; N, 14.25%.

Hydrazinolysis of compounds 5a, 6a, and 7a. General procedure: A mixture of the pyrazole derivative **5a** (0.58 g, 1 mmol) and hydrazine hydrate (10 mL) in absolute ethanol was refluxed for 10 h, and the reaction mixture was cooled. The solid that precipitated was filtered off and crystallized from ethanol to give compound **8a**.

When the earlier procedure was repeated using either **6a** or **7a**, in place of **5a**, it yielded in both cases only one and the same product namely the respective pyrazolo[4,3-*d*]pyridazine **8b**. The compounds **8a**,**b** prepared are listed in the succeeding text together with their physical constants.

3,4-Bis-(3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyridazin-6-yl)-5-methyl-1-phenylpyrazole (8a). Pale yellow crystal, (0.35 g, 60% yield), mp 240–242°C (EtOH/Dioxane); IR (KBr) ν_{max}/cm^{-1} 1633 (C═N); ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 6H, $2CH_3$), 3.30 (s, 3H, CH_3), 7.53–7.83 (m, 15H, Ar–H), 7.95 (s, 1H, Pyrazole-H-5), 9.37 (s, 1H, Pyrazole-H-5); MS *m/z* (%): 575 ($M^+ + 1$, 0.6), 433 (14), 432 (32), 406 (19), 405 (58), 149(12), 142(13), 128 (15) , 125 (11), 123 (12), 119 (112), 118 (30), 119 (11), 118 (30), 77 (100), 109 (11), 108 (20), 104(30), 95(21), 92 (80), 91 (12), 77 (100). *Anal*. Calcd for $C_{34}H_{26}N_{10}$ (574.65): C,71.06; H, 4.56; N, 24.37. Found: C, 71.22; H, 4.65; N, 24.39%.

3,4-Bis-(3-oxo-1-phenyl-1H,3H-pyrazolo[3,4-d]pyridazin-6-yl)-5-methyl-1-phenylpyrazole (8b). Pale yellow crystal, (0.37 g, 64% yield), mp 286–288°C (EtOH/Dioxane); IR (KBr) ν_{max}/cm^{-1} 3434 (NH), 1677 (C═O), 1638 (C═N); ^{1}H NMR ($CDCl_3$): 3.29 (s, 3H, CH_3), 7.10–7.31 (m, 15H, Ar–H), 7.90 (s, 1H, pyrazole-H-5), 9.40 (s, 1H, pyrazole-H-5), 12.46 (s, 2H, 2NH); MS *m/z* (%): 580 ($M^+ + 2$, 0.15), 394 (20), 143 (21), 118 (39), 104 (27), 93 (100), 77 (70). *Anal*. Calcd for $C_{32}H_{22}N_{10}O_2$ (578.60): C, 66.43; H, 3.83; N, 24.21. Found: C, 66.70; H, 3.90; N, 24.50%.

Synthesis of 1,4,5-trimethyl-6-phenyl-6H-pyrazolo[3,4-d]-pyridazine (10). A mixture of the pyrazole derivative **3a** (0.25 g, 1 mmol) and hydrazine hydrate (10 mL) in absolute ethanol was refluxed for 10 h, and the reaction mixture was cooled. The solid that precipitated was filtered off and crystallized from ethanol to give compound **10** as white solid, 0.15 g, 63% yield, mp 254–256°C (EtOH) (Lit. mp 239–40°C [37]). IR (KBr) ν_{max}/cm^{-1} 1634 (C═N); ^{1}H NMR ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 2.89 (s, 6H, $2CH_3$), 7.49–7.63 (m, 5H, Ar–H); MS *m/z* (%): 238 (M^+, 100), 117 (13), 141 (12), 77 (45). *Anal*. Calcd for $C_{14}H_{14}N_4$ (238.29): C, 70.75; H, 5.92; N, 23.51. Found: C, 70.79; H, 6.02; N, 23.55%.

Synthesis of bis-enamine 11. A mixture of compound **10** (1.5 g, 6.3 mmol) and DMF–DMA (4 g) was refluxed for 20 h then left to cool. Methanol was added to cold mixture. The resulting solid was collected by filtration, washed with methanol, dried, and finally crystallized from ethanol to afford the enaminone **11** as pale orange solid, (1.7 g, 78% yield), mp 242–244°C; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H, CH_3), 2.87 (s, 6H, $N(CH_3)_2$), 2.93 (s, 6H, $N(CH_3)_2$), 5.86 (d, *J* = 13 Hz, 2H, ═CH), 7.50–7.59 (m, 5H, ArH), 7.61 (d, *J* = 13 Hz, 2H, ═CH); MS *m/z* (%): 348 (M^+, 0.74), 238 (32), 149 (22), 141 (11.26), 118 (28.31), 104 (32.7), 98 (20), 77 (45), 46 (100). *Anal*. Calcd for $C_{20}H_{24}N_6$ (348.45): C, 68.94; H, 6.94; N, 24.12. Found: C, 69.05; H, 7.10; N, 24.25%.

Synthesis of 3,6-bis-(3-acetyl-1-phenyl-1H-pyrazol-4-yl)-5-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyridazine (9a). To a stirred solution of *bis*-enamine **11** (0.39 g, 1 mmol) and the hydrazonoyl chloride **1a** (0.392 g, 2 mmol) in dry benzene (20 mL), triethylamine (0.2 mL) was added, and the mixture was refluxed for 20 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with methanol. The solid product, so formed in each case, was collected by filtration,

washed with water, dried, and crystallized from ethanol to give compound **9a** as orange solid, (0.52 g, 90% yield), mp 162–164°C; IR (KBr) ν_{max}/cm^{-1} 1680 (C═O); ^1H NMR ($CDCl_3$) δ 2.57 (s, 6H, $2COCH_3$), 2.83 (s, 3H, CH_3), 7.45–7.59 (m, 15H, Ar–H), 7.83 (s, 1H, pyrazole-H-5), 9.20 (s, 1H, pyrazole-H-5); MS *m/z* (%): 502 (M^+, 2), 446 (3), 331 (37), 210 (11), 118 (24), 77 (100). *Anal*. Calcd for $C_{34}H_{26}N_8O_2$ (578.64): C, 70.58; H, 4.53; N, 19.37 Found: C, 70.90; H, 4.60; N, 19.50%.

REFERENCES AND NOTES

[1] Shawali, A. S.; Samy, N. A. The Open Bioactive Compd. J. 2009, 2, 8.
[2] Shawali, A. S. Current Org. Chem. 2010, 14, 784.
[3] Shawali, A. S.; Parkanyi, C. J. Heterocycl. Chem. 1980, 17, 833.
[4] Shawali, A. S. Heterocycles 1983, 20, 2239.
[5] Shawali, A. S. Chem Rev 1993, 93, 2731.
[6] Shawali, A. S.; Abdallah, M. A. Adv Heterocycl Chem 1995, 63, 277.
[7] Shawali, A. S.; Elsheikh, S. M. J Heterocycl. Chem. 2001, 38, 541.
[8] Shawali, A. S.; Mosselhi, M. A. N. J. Heterocycl. Chem. 2003, 40, 725.
[9] Shawali, A. S.; Mosselhi, M. A. N. J. Sulfur. Chem. 2005, 26, 267.
[10] Shawali, A. S.; Edrees, M. M. Arkivoc 2006, ix, 292.
[11] Shawali, A. S.; Sherif, S. M. Current Org. Chem. 2007, 11, 773.
[12] Shawali, A. S.; Farghaly, T. M. Arkivoc 2008, i, 18.
[13] Abushanab, F. A.; Sherif, S. M.; Mousa, S. A. S. J. Heterocycl. Chem. 2009, 45, 801.
[14] Edafiogho, I. O., *et al*, J Pharm Sci 2007, 96, 2509.
[15] Svete, J. Arkivoc 2006, vii, 35.
[16] Palmieri, G.; Cimarelli, C. Arkivoc 2006, vi, 104.
[17] Negri, G.; Kascheres, C. M.; Kascheres, A. J. J. Heterocycl. Chem. 2004, 41, 461.
[18] Shawali, A. S.; Farghaly, T. A.; Al-Dahshoury, A. R. Arkivoc 2009, xiv, 88.
[19] Kascheres, C. M. J. Braz. Chem. Soc. 2003, 14, 945.
[20] Alassar, A. A.; El-Khair, A. A. Tetrahedron 2003, 59, 8463.
[21] Lui, P.; Greenhill, J. V. Adv Heterocycl Chem 1997, 67, 207.
[22] Bejan, E.; Haddou, H. A.; Daran, J. C.; Balavoine, G. G. A. Synth. 1996, 1012.
[23] Cochman, S. M.; Jeffery, J. C.; Ward, M. D. Polyhedron 1999, 18, 2633.
[24] Hassanien, A. A. J. Chem. Res. 2004, 536.
[25] Bejan, E.; Ait.Haddou, H.; Daran, J. C.; Balavoine, G. G. A. Eur. J. Org. Chem. 1998, 2907.
[26] Pezet, F.; Routaboul, L.; Daran, J. C.; Sasaki, I.; Ait.Haddou, H.; Daran, J. C.; Balavoine, G. G. A. Tetrahedron 2000, 56, 8489.
[27] Bark, T.; Evans, H. S.; Zelewsky, A. V. J. Chem. Soc. (P1) 2002, 1881.
[28] Kleenmann, J.; Engel, B.; Kutscher, D.; Reichert, D. Pharmaceutical Substances; Thieme, New York. 1999.
[29] Bruno, O.; Ranise, A.; Bondavalli, F.; Schenone, P.; D'Amico, M.; Filippelli, A.; Felippelli, W.; Rossi, S. Farmaco 1993, 48, 949.
[30] Cuadro, A. M.; Elguero, J.; Navarro, P. Chem Pharm Bull 1985, 33, 2535.
[31] Shawali, A. S.; Abdallah, M. A.; Moselhi, M. A.; Elewa, M. S. J Heterocycl. Chem. 2007, 44, 285.
[32] Hassaneen, H. M.; Shawali, A. S.; Elwan, N. M.; Abunada, N. M. Sulfur Lett. 1992, 13, 273.
[33] Shawali, A. S.; Moselhi, M. A.; Farghaly, T. A. J. Chem. Res. 2007, 479.
[34] Shawali, A. S.; Moselhi, M. A.; Abdallah, M. A.; Elewa, M. S. J. Chem. Res. 2008, 67.
[35] Albar, H. A. J. Chem. Res. 1996, (S), 316; (M), 1756.
[36] Tewari, R. S.; Parihar, P. Indian J Chem 1980, 19(B), 217.
[37] Albar, H. A. J. Chem. Res. 1999, (S), 182; (M), 872.