European Journal of Chemistry 4 (2) (2013) 102-109

European Journal of Chemistry

Journal homepage: www.eurjchem.com

Regioselective synthesis of some functionalized 3,4'-*bis*-(pyrazolyl)ketones and chemoselectivity in their reaction with hydrazine hydrate

Hamdi Mahmoud Hassaneen * and Ahmad Sami Shawali

Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt

**Corresponding author at: Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt. Tel.: +202.35676571; fax: +202.35676571. E-mail address: hamdi_251@yahoo.com (H. M. Hassaneen).*

ARTICLE INFORMATION

Received: 16 January 2013
Received in revised form: 02 February 2013
Accepted: 03 February 2013
Online: 30 June 2013

KEYWORDS

Enaminones
Enamino esters
Regioselectivity
Chemoselectivity
Hydrazonoyl halides
Pyrazolo[3,4-*d*]pyridazines

ABSTRACT

A new enamino ester, (*E*)-ethyl 3-(dipropylamino)acrylate, was prepared and used for synthesis of various pyrazole derivatives, 4a-k and 5a-d. Other new enaminone, (*E*)-ethyl 3-(3-(dimethylamino)acryloyl)-1-(4-nitrophenyl)-1*H*-pyrazole-4-carboxylate (8), was also prepared from compound 4a and utilized as precursor for synthesis of different functionalized 3,4'-*bis*-pyrazolyl ketones 9a-c, 10a-c. The site selectivity in hydrazinolysis of the latter was studied. The structures of the products namely pyrazolo[3,4-*d*]pyridazine derivatives 11(13) were confirmed by spectral and elemental analyses and by alternate unambiguous synthesis.

1. Introduction

A literature survey reveals that hydrazonoyl halides are useful versatile precursors for synthesis of numerous heterocyclic compounds. Their chemistry has attracted the interest of many research groups all over the world. At present, there are several review articles by Shawali *et al.* covering their reactions and applications [1-9]. Also, literature reports indicate that many pyrazole derivatives found use in various pharmaceutical, agrochemical and many other applications [10-17]. In the light of these facts and in conjunction with our ongoing studies of the chemistry of hydrazonoyl halides, it was thought interesting to study the 1,3-dipolar cycloaddition of the nitrilimines derived from hydrazonoyl halides to the enamino ester, namely (*E*)-ethyl 3-(dipropylamino)-acrylate **1**, which has not been reported hitherto. Our objectives after such a study are on one hand to explore the utility of the resulting pyrazole cycloadducts (**4a-k**, **5a-d**), expected from the target reaction (Scheme 1) in synthesis of new functionalized 3,4'-*bis*(pyrazolyl)ketones **9** and **10** (Scheme 2 and 3) and on the other hand to explore the site selectivity in hydrazinolysis of the latter heterocyclic compounds **9**.

2. Experimental

2.1. Instrumentation

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried prior their use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts were related to that of the solvent DMSO-d_6. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses of the products were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Hydrazonoyl halides were prepared following literature procedures [18-24]. DMF-DMA, dipropylamine and ethyl propiolate were purchased from Merck Company.

2.2. Synthesis

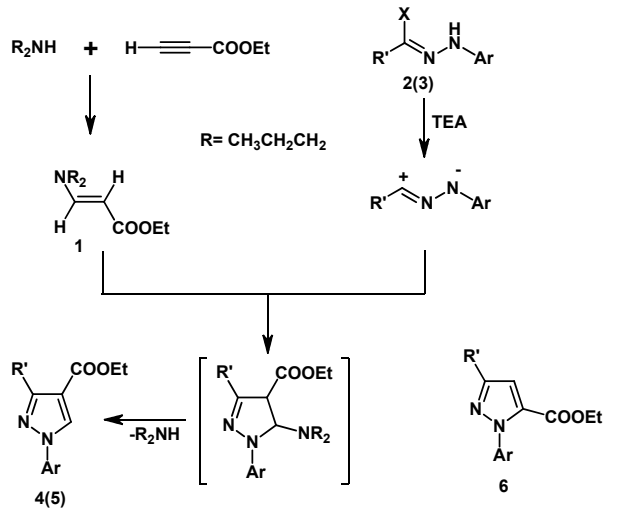
2.2.1. Preparation of (E)-ethyl 3-(dipropylamino)acrylate (1)

To a solution of ethyl propiolate (9.8 g, 0.1 mol) in methanol (50 mL) was added a solution of dipropylamine (10.1 g, 0.1 mol) in methanol (50 mL) dropwise over a period of 30 min while being stirred. The reaction mixture was stirred for further 1 h and then the solvent was distilled under reduced pressure. The enamino ester, **1**, was obtained as oil (Scheme 1). Color: Pale yellow. Yield: 90%. FT-IR (KBr, cm^{-1}): 1686 ν(C=O), 1608 ν(C=C). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.79 (t, *J* = 7 Hz, 6H, $(CH_3CH_2CH_2)_2N$), 1.15 (t, *J* = 8 Hz, 3H, CH_3CH_2O), 1.47 (m, 4H, $(CH_3CH_2CH_2)_2N$), 2.97 (t, *J* = 8 Hz, 4H, $(CH_3CH_2CH_2)_2N$), 4.02 (q, *J* = 7 Hz, 2H, CH_3CH_2O), 4.42 (d, *J* = 13.2 Hz, 1H, =CH-CO), 7.36 (d, *J* = 13.2 Hz, 1H, =CH-N$(CH_2CH_2CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 11.1, 14.6, 50.3, 58.6, 63.3, 126.1, 151.7, 169.8. Anal. calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.10; H, 10.42; N, 6.82%.

2.2.2. Synthesis of ethyl 1-aryl-3-substituted-1H-pyrazole-4-carboxylates (4a-k, 5a-d)

General procedure: To an equimolar mixture (5 mmol each) of the (*E*)-ethyl 3-(dipropylamino)acrylate, **1**, and the appropriate hydrazonoyl halide **2**(**3**) in dioxane (50 mL) was

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
DOI:10.5155/eurjchem.4.2.102-109.723



2(4)	R'	Ar	3(5)	R'	Ar
a	CH_3CO	4-NO_2-C_6H_4	a	C_6H_5CH=CH	C_6H_5
b	2-Thenoyl	C_6H_5	b	2-Furyl	4-NO_2-C_6H_4
c	2-Thenoyl	4-Cl-C_6H_4	c	2-Thienyl	4-NO_2-C_6H_4
d	2-Thenoyl	4-NO_2-C_6H_4	d	C_2H_5COO	4-NO_2-C_6H_4
e	C_6H_5CO	C_6H_5			
f	C_6H_5CO	4-CH_3-C_6H_4			
g	C_6H_5CO	4-Cl-C_6H_4			
h	2-Naphthoyl	C_6H_5			
i	2-Naphthoyl	4-CH_3-C_6H_4			
j	2-Naphthoyl	4-Cl-C_6H_4			
k	2-Naphthoyl	4-NO_2-C_6H_4			

Scheme 1

added triethylamine (1.0 g, 10 mmol) and the reaction mixture was refluxed for 4 h, then the solvent was distilled under reduced pressure. To the residue left, ethanol was added and the solid produced was collected and crystallized from the appropriate solvent to give the corresponding pyrazole derivative. The compounds prepared together with their physical constants are given below (Scheme 1).

Ethyl 3-acetyl-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**4a**): Color: Golden yellow crystals. Yield: 78% (EtOH). M.p.: 160-162 °C. FT-IR (KBr, cm^{-1}): 3120 ν(CH), 1735, 1697 ν(C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.36 (t, *J* = 7.2 Hz, 3H, C*H*$_3$CH$_2$O), 2.69 (s, 3H, CH_3CO), 4.33 (q, *J* = 7.5 Hz, 2H, CH_3C*H*$_2$O), 7.97 (d, *J* = 9 Hz, 2H, Ar-H), 8.97 (d, *J* = 9 Hz, 2H, Ar-H), 8.39 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 14.06, 28.67, 61.26, 117.17, 119.68, 125.38, 132.09, 142.92, 146, 67, 151.90, 161.36, 193.04. MS (EI, *m/z* (%)): 303 (M^+, 48), 288 (26), 260 (100). Anal. calcd. for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.21; H, 4.31; N, 13.65%.

Ethyl 1-phenyl-3-(thiophene-2-carbonyl)-1H-pyrazole-4-carboxylate (**4b**): Color: Yellow crystals. Yield: 70% (MeOH). M.p.: 89-90 °C. FT-IR (KBr, cm^{-1}): 3144 ν(CH), 1697, 1640 ν(C=O). ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ, ppm):1.37 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$O), 4.14 (q, *J* = 7.5 Hz, 2H, CH_3C*H*$_2$O), 7.25-8.19 (m, 8H, Ar-H), 9.11 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ, ppm): 14.00, 60.72, 115.97, 119.72, 121.12, 128.22, 129.13, 129.89, 132.50, 136.66, 138.60, 142.87, 150.24, 161.51, 180.44. Anal. calcd. for $C_{17}H_{14}N_2O_3S$: C, 62.57; H, 4.32; N, 8.59; S. 9.81. Found: C, 62.65; H, 4.41; N, 8.41; S, 9.70%.

Ethyl 1-(4-chlorophenyl)-3-(thiophene-2-carbonyl)-1H-pyrazole-4-carboxylate (**4c**): Color: Colorless crystals. Yield: 75% (EtOH). M.p.: 129-130 °C. FT-IR (KBr, cm^{-1}): 3124 ν(CH), 1705, 1631 ν(C=O). ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ, ppm): 1.16 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.17 (q, *J* = 7 Hz, 2H, CH_3C*H*$_2$O), 7.27 (m, 1H, Ar-H), 7.61 (d, *J* = 9 Hz, 2H, Ar-H), 7.68 (m, 1H, Ar-H), 8.01 (d, *J* = 9 Hz, 2H, Ar-H), 8.17 (m, 1H, Ar-H), 9.24 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ, ppm): 13.82, 60.41, 115.80, 120.87, 128.93, 129.57, 132.24, 132.72, 136.58, 136.77, 137.27, 142.58, 150.14, 161.09, 180.04. MS (EI, *m/z* (%)): 362 (M^++2, 4), 360 (M^+, 13), 314 (16), 138 (15), 111 (100). Anal. calcd. for $C_{17}H_{13}ClN_2O_3S$: C, 56.60; H, 3.63; N, 7.77; S, 8.87. Found: C, 56.51; H, 3.41; N, 7.57; S, 8.62%.

Ethyl 1-(4-nitrophenyl)-3-(thiophene-2-carbonyl)-1H-pyrazole-4-carboxylate (**4d**): Color: Yellow crystals. Yield: 80% (MeCN). M.p.: 178-80 °C. FT-IR (KBr, cm^{-1}): 1695, 1654 ν(C=O). ^{1}H NMR (300 MHz, DMSO-*d6*, δ, ppm): 1.16 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.18 (q, *J* = 7 Hz, 2H, CH_3C*H*$_2$O), 7.29 – 8.26 (m, 3H, Ar-H), 8.29 (d, *J* = 9 Hz, 2H, Ar-H), 8.40 (d, *J* = 9 Hz, 2H, Ar-H), 9.43 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ, ppm): 13.76, 60.52, 116.39, 120.06, 120.62, 125.24, 128.96, 133.53, 136.79, 136.99, 142.40, 142.75, 146.07, 150.88, 160.85. MS (EI, *m/z* (%)): 371 (M^+, 11), 327 (25), 326 (19), 111 (100). Anal. calcd. for $C_{17}H_{13}N_3O_5S$: C, 54.99; H, 3.53; N, 11.32; S, 8.62. Found: C, 54.81; H, 3.41; N, 11.22, S, 8.41%.

Ethyl 3-benzoyl-1-phenyl-1H-pyrazole-4-carboxylate (**4e**): Color: Yellow crystals. Yield: 65% (EtOH). M.p.: 102-103 °C. FT-IR (KBr, cm^{-1}): 3116 ν(CH), 1735, 1690 ν(C=O). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm):1.16 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.21 (q, *J* = 7 Hz, 2H, CH_3C*H*$_2$O), 7.38-7.91 (m, 10H, Ar-H), 9.11 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 320 (M^+, 25), 319 (20), 105 (100), 77 (75). Anal. calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.91; H, 4.91; N, 8.42%.

Ethyl 3-benzoyl-1-(p-tolyl)-1H-pyrazole-4-carboxylate (**4f**): Color: Colorless crystals. Yield: 75% (EtOH). M.p.: 148-150 °C. FT-IR (KBr, cm^{-1}): 1710, 1669 ν(C=O). ^{1}H NMR (300 MHz, DMSO-*d*$_6$, δ, ppm): 1.04 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 2.35 (s, 3H, Ar-CH_3), 4.10 (q, *J* = 7 Hz, 2H, CH_3C*H*$_2$O), 7.33-7.91 (m, 9H, Ar-H), 9.17 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-*d*$_6$, δ, ppm): 13.6, 20.4, 60.2, 115.3, 119.3, 128.7, 129.4, 129.9, 131.9, 133.8, 136.2, 136.3, 137.4, 150.5, 161.1, 189.2. MS (EI, *m/z* (%)): 334 (M^+, 28), 289 (17), 105 (100), 91 (15), 77 (71). Anal. calcd. for

$C_{20}H_{18}N_2O_3$ (334.38): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.71; H, 5.31; N, 8.22%.

Ethyl 3-benzoyl-1-(4-chlorophenyl)-1H-pyrazole-4-carboxylate (**4g**): Color: Colorless crystals. Yield: 75% (EtOH). M.p.: 148-150 °C. FT-IR (KBr, cm^{-1}): 3116 ν(CH), 1709, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.09 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.15 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.33-8.01 (m, 9H, Ar-H), 9.20 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 356 (M^++2, 10), 354 (M^+, 31), 309 (21), 138 (10), 105 (100), 77 (83). Anal. calcd. for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.11; H, 4.22; N, 7.82%.

Ethyl 3-(2-naphthoyl)-1-phenyl-1H-pyrazole-4-carboxylate (**4h**): Color: Yellow crystals. Yield: 73% (EtOH). M.p.: 122-124 °C. FT-IR (KBr, cm^{-1}): 1716, 1678 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.97 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.05 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.42-8.01 (m, 11H, Ar-H), 8.42 (s, 1H, Ar-H), 9.20 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.57, 60.28, 115.61, 119.35, 123.88, 126.99, 127.60, 127.80, 128.46, 129.06, 129.56, 131.62, 131.83, 132.04, 132.48, 133.68, 135.28, 138.36, 150.90, 161.23, 189.35. MS (EI, *m/z* (%)): 370 (M^+, 52), 341 (11), 325 (29), 297 (12), 155 (76), 127 (100), 104 (22), 77 (49). Anal. calcd. for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.32; H, 4.71; N, 7.33%.

Ethyl 3-(2-naphthoyl)-1-(p-tolyl)-1H-pyrazole-4-carboxylate (**4i**): Color: Yellow crystals. Yield: 80% (EtOH). M.p.: 115-116 °C. FT-IR (KBr, cm^{-1}): 1718, 1685 ν(C=O).^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm):0.97 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 2.41 (s, 3H, Ar-CH$_3$), 4.01 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.42-8.08 (m, 10H, Ar-H), 8.42 (s, 1H, Ar-H), 9.11 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 384 (M^+, 60), 383 (42), 155 (70), 127 (100), 91 (26). Anal. calcd. for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 75.02; H, 5.01; N, 7.44%.

Ethyl 3-(2-naphthoyl)-1-(4-chlorophenyl)-1H-pyrazole-4-carboxylate (**4j**): Color: Colorless crystals. Yield: 75% (MeCN). M.p.: 132-134 °C. FT-IR (KBr, cm^{-1}): 1701, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.95 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.01 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.52-8.04 (m, 10H, Ar-H), 8.41 (s, 1H, Ar-H), 9.17 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.58, 60.35, 115.80, 120.81, 123.83, 127.06, 127.64, 128.50, 129.14, 129.49, 129.65, 131.85, 132.20, 132.29, 132.45, 133.60, 135.32, 137.20, 151.06, 161.13, 189.23. MS (EI, *m/z* (%)): 406 (M^++2, 17), 404 (M^+, 44), 359 (29), 249 (17), 154 (51), 138 (22), 127 (100). Anal. calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23; N, 6.92. Found: C, 68.11; H, 4.11; N, 6.72%.

Ethyl 3-(2-naphthoyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**4k**): Color: Yellow crystals. Yield: 80% (DMF). M.p.: 200-202 °C. FT-IR (KBr, cm^{-1}): 1701, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.98 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.04 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.59-8.40 (m, 10H, Ar-H), 8.43 (s, 1H, Ar-H), 9.40 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 415 (M^+, 47), 370 (18), 260 (14), 155 (82), 127 (100), 77 (18). Anal. calcd. for $C_{23}H_{17}N_3O_5$: C, 66.50; H, 4.13; N, 10.12. Found: C, 66.71; H, 4.01; N, 10.21%.

(E)-Ethyl 1-phenyl-3-styryl-1H-pyrazole-4-carboxylate (**5a**): Color: Pale yellow crystals. Yield: 73% (EtOH). M.p.: 104-106 °C. FT-IR (KBr, cm^{-1}): 3128 ν(CH), 1705 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.32 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.28 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.28-7.95 (m, 12H, Ar-H, HC=CH), 8.95 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.40, 60.27, 113.52, 117.86, 119.27, 126.81, 127.58, 128.53, 129.04, 129.73, 132.11, 132.55, 136.49, 138.85, 150.23, 162.73. MS (EI, *m/z* (%)): 318 (M^+, 94), 317 (100), 289 (16), 271 (22), 245 (31), 140 (11), 115 (14), 77 (92). Anal. calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.61; H, 5.82; N, 8.61%.

Ethyl 3-(furan-2-yl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**5b**): Color: Yellow crystals. Yield: 78% (DMF). M.p.: 198-200 °C. FT-IR (KBr, cm^{-1}): 3124 ν(CH), 1686 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.30 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.3 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 6.6 (m, 1H, furan-H), 7.38 (m, 1H, furan-H), 7.79 (m, 1H, furan-H), 8.33 (d, *J* = 9 Hz, 2H, Ar-H), 8.36 (d, *J* = 9 Hz, 2H, Ar-H), 9.20 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 327 (M^+, 100), 299 (14), 282 (47), 270 (19), 255 (15), 236 (25), 103 (12). Anal. calcd. for $C_{16}H_{13}N_3O_5$: C, 58.72; H, 4.00; N, 12.84. Found: C, 58.91; H, 4.12; N, 12.60%.

Ethyl 1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carboxylate (**5c**): Color: Golden yellow crystals. Yield: 82% (AcOH). M.p.: 178-180 °C. FT-IR (KBr, cm^{-1}): 3120 ν(CH), 1718 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.30 (t, *J* = 7 Hz, 3H, CH_3CH$_2$O), 4.26 (q, *J* = 7 Hz, 2H, CH$_3$CH_2O), 7.14 (m, 1H, thiophene-H), 7.61 (m, 1H, thiophene-H), 8.04 (m, 1H, thiophene-H), 8.29 (d, *J* = 9 Hz, 2H, Ar-H), 8.32 (d, *J* = 9 Hz, 2H, Ar-H), 9.15 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 343 (M^+, 100), 315 (21), 298 (54), 252 (33), 120 (13). Anal. calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.98; H, 3.82; N, 12.24; S, 9.32. Found: C, 55.71; H, 3.62; N, 12.01; S, 9.41%.

Diethyl 1-(4-nitrophenyl)-1H-pyrazole-3, 4-dicarboxylate (**5d**): Color: Pale yellow crystals. Yield: 82% (EtOH). M.P.: 148-150 °C. FT-IR (KBr, cm^{-1}): 3133 ν(CH), 1743, 1702 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.25-133 (2t, *J* = 7 Hz, 6H, 2 CH_3CH$_2$O), 4.24-4.35 (2q, *J* = 7 Hz, 4H, 2 CH$_3$CH_2O), 8.14 (d, *J* = 9 Hz, 2H, Ar-H), 8.36 (d, *J* = 9 Hz, 2H, Ar-H), 9.23 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.13, 14.24, 61.15, 62.05, 116.47, 120.23, 125.53, 133.42, 142.80, 145.92, 146.39, 161.10, 161.79. Anal. calcd. for $C_{15}H_{15}N_3O_6$ (333.30): C, 54.05; H, 4.54; N, 12.61. Found: C, 54.21; H, 4.33; N, 12.41%.

2.2.3. Synthesis of 2-aryl-7-substituted-2H-pyrazolo[3,4-d] pyridazin-4(5H)-ones (7a-k)

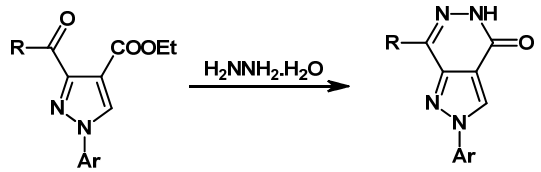
A mixture of the appropriate ethyl 1-aryl-3-substituted-1*H*-pyrazole-4-carboxylate **4a-k** (3 mmol) and hydrazine hydrate (13 g, 3 mmol) in ethanol (30 mL) was refluxed 1 h and then cooled. The product that was separated was filtered off and crystallized from the appropriate solvent to give the corresponding product **7**. The compounds prepared together with their physical constants are listed below (Scheme 2).

7-Methyl-2-(4-nitrophenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7a**): Color: Colorless crystals. Yield: 78% (DMF). M.p.: 358-360 °C. FT-IR (KBr, cm^{-1}): 3259 ν(NH), 1666 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.50 (s, 3H, CH$_3$), 8.20 (d, *J* = 6 Hz, 2H, Ar-H), 8.42 (d, *J* = 6 Hz, 2H, Ar-H), 9.50 (s, 1H, =CH-N), 11.95 (s, 1H, NH). MS (EI, *m/z* (%)): 271 (M^+, 100), 213 (21), 149 (14), 127 (20), 103 (16). Anal. calcd. for $C_{12}H_9N_5O_3$: C, 53.14; H, 3.34; N, 25.82. Found: C, 52.91; H, 3.12; N, 25.51%.

2-Phenyl-7-(thiophen-2-yl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7b**): Color: Colorless crystals. Yield: 81% (DMF). M.p.: 228-230 °C. FT-IR (KBr, cm^{-1}): 3240 ν(NH), 1684 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.21-8.34 (m, 9H, Ar-H, NH), 9.43 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 78.91, 116.28, 120.41, 120.91, 127.85, 127.93, 128.11, 129.80, 135.11, 136.98, 138.68, 144.1, 157.90. MS (EI, *m/z* (%)): 294 (M^+, 100), 237 (26), 151 (16), 149 (12), 77 (83). Anal. calcd. for $C_{15}H_{10}N_4OS$: C, 61.22; H, 3.43; N, 19.04; S, 10.87. Found: C, 61.01; H, 3.11; N, 18.73; S, 10.61%.

2-(4-Chlorophenyl)-7-(thiophen-2-yl)-2H-pyrazolo[3,4-d] pyridazin-4(5H)-one (**7c**): Color: Pale yellow crystals. Yield: 83% (DMF). M.p.: 272-274 °C. FT-IR (KBr, cm^{-1}): 3230 ν(NH), 1684 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.2 (m, 1H, Ar-H), 7.50-8.10 (m, 6H, Ar-H, NH), 8.34 (m, 1H, Ar-H), 9.43 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 78.91, 116.28, 120.41, 120.91, 127.85, 127.93, 128.11, 129.80, 135.11, 136.98, 138.68, 144.1, 157.90. MS (EI, *m/z* (%)): 330 (M^++2, 38), 328 (M^+, 100), 271 (19), 138 (12), 111 (61). Anal. calcd. for $C_{15}H_9ClN_4OS$: C, 54.81; H, 2.76; N, 17.04; S, 9.73. Found: C, 54.61; H, 2.56; N, 17.34; S, 9.51%.

2-(4-Nitrophenyl)-7-(thiophen-2-yl)-2H-pyrazolo[3,4-d] pyridazin-4(5H)-one (**7d**): Color: Yellow crystals. Yield: 80% (DMF). M.P.: >360 °C. FT-IR (KBr, cm^{-1}): 3336 ν(NH), 1682 ν(C=O). MS (EI, *m/z* (%)): 339 (M^+, 100), 338 (37), 132 (16), 111 (21), 103 (12), 83 (14). Anal. calcd. for $C_{15}H_9N_5O_3S$: C, 53.10; H, 2.67; N, 20.64; S, 9.43. Found: C, 52.81; H, 2.41; N, 20.51; S, 9.61%.



4(7)	R	Ar
a	CH_3	4-NO_2-C_6H_4
b	2-Thinyl	C_6H_5
c	2-Thinyl	4-Cl-C_6H_4
d	2-Thinyl	4-NO_2-C_6H_4
e	C_6H_5	C_6H_5
f	C_6H_5	4-CH_3-C_6H_4
g	C_6H_5	4-Cl-C_6H_4
h	2-Naphthyl	C_6H_5
i	2-Naphthyl	4-CH_3-C_6H_4
j	2-Naphthyl	4-Cl-C_6H_4
k	2-Naphthyl	4-NO_2-C_6H_4

Scheme 2

2,7-Diphenyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7e**): Color: Colorless crystals. Yield: 85% (DMF). M.p.: 228-230 °C. FT-IR (KBr, cm^{-1}): 3230 ν(NH), 1671 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.49-8.34 (m, 10H, Ar-H), 9.45 (s, 1H, =CH-N), 12.54 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 117, 120.8, 127.8, 128.0, 128.7, 129.1, 129.7, 130.1, 135.0, 139.0, 139.01, 145.4, 158.4. MS (EI, *m/z* (%)): 288 (M^+, 100), 211 (28), 155 (12), 128 (12), 77 (96). Anal. calcd. for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.55; H, 4.01; N, 19.10%.

7-Phenyl-2-(p-tolyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7f**): Color: Colorless crystals. Yield: 84% (DMF). M.p.: 262-264 °C. FT-IR (KBr, cm^{-1}): 3199 ν(NH), 1667 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.49 (s, 3H, Ar-CH_3), 7.41- 8.32 (m, 9H, Ar-H), 9.37 (s, 1H, =CH-N), 12.51 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 20.5, 116.5, 120.2, 120.8, 127.2, 127.5, 128.4, 129.3, 130.0, 133.7, 136.4, 138.4, 144.9, 158.1. MS (EI, *m/z* (%)): 302 (M^+, 100), 301 (64), 245 (16), 210 (17), 185 (12), 129 (13), 91 (77), 77 (33). Anal. calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.41; H, 4.52; N, 18.22%.

2-(4-Chlorophenyl)-7-phenyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7g**): Color: Pale yellow crystals. Yield: 85% (DMF). M.p.: 296-298 °C. FT-IR (KBr, cm^{-1}): 3221 ν(NH), 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.3-8.2 (m, 9H, Ar-H), 9.41 (s, 1H, =CH-N), 12.4 (s, 1H, NH). MS (EI, *m/z* (%)): 324 (M^++2, 24), 322 (M^+, 100), 321 (27), 211 (29), 185 (13), 127 (14), 111 (36), 77 (23). Anal. calcd. for $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.11; H, 3.22; N, 17.61%.

7-(Naphthalen-2-yl)-2-phenyl-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**7h**): Color: Colorless crystals. Yield: 85% (DMF). M.p.: 259-261 °C. FT-IR (KBr, cm^{-1}): 3210 ν(NH), 1675 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.51-8.33 (m, 11H, Ar-H), 9.04 (s, 1H, Ar-H), 9.46 (s, 1H, =CH-N), 12.61 (s, 1H, NH). MS (EI, *m/z* (%)): 338 (M^+, 100), 337 (15), 261 (16), 176 (12), 127 (16), 77 (64). Anal. calcd. for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.31; H, 3.92; N, 16.62%.

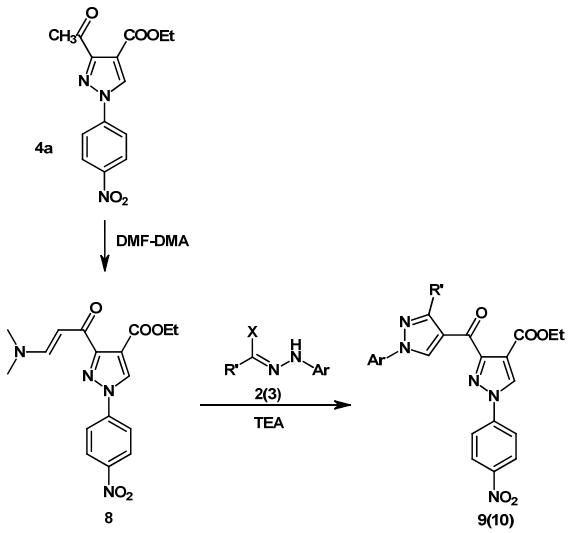
7-(Naphthalen-2-yl)-2-(p-tolyl)-2H-pyrazolo[3,4-d] pyridazin-4(5H)-one (**7i**): Color: Colorless crystals. Yield: 85% (DMF). M.p.: 280-282 °C. FT-IR (KBr, cm^{-1}): 3212 ν(NH), 1677 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.4 (s, 3H, Ar-CH_3), 7.41-8.31 (m, 10H, Ar-H), 9.1 (s, 1H, Ar-H), 9.33 (s, 1H, =CH-N), 12.55 (s, 1H, NH). MS (EI, *m/z* (%)): 352 (M^+, 100), 351 (20), 295 (11), 261 (11), 176 (16), 127 (9), 91 (40). Anal. calcd. for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 74.72; H, 4.33; N, 15.70%.

2-(4-Chlorophenyl)-7-(naphthalen-2-yl)-2H-pyrazolo[3,4-d] pyridazin-4(5H)-one (**7j**): Color: Colorless crystals. Yield: 82% (DMF). M.p.: 286-288 °C. FT-IR (KBr, cm^{-1}): 3215 ν(NH), 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.71-8.31 (m, 10H, Ar-H), 9.10 (s, 1H, Ar-H), 9.41 (s, 1H, =CH-N), 12.59 (s, 1H, NH). MS (EI, *m/z* (%)): 374 (M^++2, 36), 372 (M^+, 100), 371 (26), 261 (14), 176 (14), 151 (10), 127 (18), 111 (27). Anal. calcd. for $C_{21}H_{13}ClN_4O$: C, 67.66; H, 3.51; N, 15.03. Found: C, 67.41; H, 3.21; N, 14.88%.

7-(Naphthalen-2-yl)-2-(4-nitrophenyl)-2H-pyrazolo[3,4-d] pyridazin-4(5H)-one (**7k**): Color: Yellow crystals. Yield: 83% (DMF). M.p.: 354-356 °C. FT-IR (KBr, cm^{-1}): 3320 ν(NH), 1680 ν(C=O). MS (EI, *m/z* (%)): 383 (M^+, 100), 382 (35), 279 (9), 261 (15), 168 (12), 127 (17). Anal. calcd. for $C_{21}H_{13}N_5O_3$: C, 65.79; H, 3.42; N, 18.27. Found: C, 65.71; H, 3.35; N, 18.04%.

2.2.4. Synthesis of (E)-ethyl 3-(3-(dimethylamino)acryloyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (8)

To a solution of ethyl 3-acetyl-1-(4-nitrophenyl)-1*H*-pyrazole-4-carboxylate **4a**, (6 g, 20 mmol) in dioxane (50 mL), DMF-DMA (2.36 g, 20 mol) was added. The reaction mixture was refluxed for 6 h and then cooled to room temperature. The solid that precipitated was filtered off and crystallized from acetonitrile to give the enaminone **8** (Scheme 3). Color: Yellow crystals. Yield: 75% (DMF). M.p.: 198-200 °C. FT-IR (KBr, cm^{-1}): 1700 ν(C=O), 1647 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.27 (t, *J* = 7 Hz, 3H, CH_3CH_2O), 3.14 (s, 6H, $(CH_3)_2N$), 4.22 (q, *J* = 7 Hz, 2H, CH_3CH_2O), 6.27 (d, *J* = 13 Hz, 1H, =CH-CO), 8.0 (d, *J* = 7 Hz, 2H, Ar-H), 8.21 (d, *J* = 7 Hz, 2H, Ar-H), 8.76 (d, *J* = 13 Hz, 1H, =C*H*-N$(CH_3)_2$), 9.15 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 358 (M^+, 31), 341 (27), 295 (100), 260 (49), 245 (19), 199 (16), 180 (16), 138 (20). Anal. calcd. for $C_{17}H_{18}N_4O_5$ (358.35): C, 56.98; H, 5.06; N, 15.63. Found: C, 56.71; H, 4.92; N, 15.41%.



9	R'	Ar	10	R'	Ar
a	C_6H_5CO	C_6H_5	a	C_6H_5CH=CH	C_6H_5
b	2-Naphthoyl	C_6H_5	b	2-Furyl	4-NO_2-C_6H_4
c	CH_3CO	C_6H_5	c	2-Thienyl	4-NO_2-C_6H_4

Scheme 3

2.2.5. Synthesis of ethyl 3-(1-aryl-3-substituted-1H-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylates (9a-c, 10a-c)

To a mixture of the appropriate hydrazonoyl halide **2e**, **2h**, **2l** and **3a-c** (3 mmol) and (*E*)-ethyl 3-(3-(dimethylamino) acryloyl)-1-(4-nitrophenyl)-1*H*-pyrazole-4-carboxylate **8** (1.07 g, 3 mmol) in dioxane was added triethylamine (0.6 g, 6 mmol) and the mixture was refluxed for 5 h, then cooled. The triethylamine hydrochloride that precipitated was filtered off. The filtrate was distilled under reduced pressure and the

residue left was triturated with ethanol (15 mL) and the solid that produced was collected and crystallized from the appropriate solvent to give the corresponding *bis*-3,4'-pyrazolyl derivative. The compounds prepared together with their physical constants are listed below (Scheme 3).

Ethyl 3-(3-benzoyl-1-phenyl-1H-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**9a**): Color: Golden yellow crystals. Yield: 72% (MeCN). M.p.: 166-168°C. FT-IR (KBr, cm^{-1}): 1715, 1697, 1662 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.21 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.22 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 7.64-8.30 (m, 14H, Ar-H), 9.20 (s, 1H, =CH-N), 9.37 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.8, 60.5, 112.4, 116.5, 119.4, 119.8, 123.6, 125.1, 128.1, 128.7, 129.4, 129.7, 133.6, 133.7, 136.0, 136.7, 138.4, 142.5, 145.9, 151.3, 180.0, 188.9. MS (EI, *m/z* (%)): 535 (M$^+$, 18), 489 (9), 385 (8), 275 (13), 105 (82), 77 (100). Anal. calcd. for $C_{29}H_{21}N_5O_6$: C, 65.04; H, 3.95; N, 13.08. Found: C, 64.81; H, 3.77; N, 12.79.

Ethyl 3-(3-(2-naphthoyl)-1-phenyl-1H-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**9b**): Color: Pale yellow crystals. Yield: 80% (DMF). M.p.: 258-260 °C. FT-IR (KBr, cm^{-1}): 1732, 1690, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.17 (t, *J* = 7 Hz, 3H, CH$_3$CH$_2$O), 4.14 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 7.46-8.05 (m, 15H, Ar-H), 8.46 (s, 1H, Ar-H), 9.23 (s, 1H, =CH-N), 9.44 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.9, 60.5, 116.4, 119.8, 120.9, 121.0123.7, 123.9, 124.7, 126.9, 127.5, 128.1, 128.4, 129.0, 129.7, 129.8, 131.8, 132.6, 133.4, 133.7, 135.2, 138.4, 142.2, 145.6, 151.4, 151.7, 160.7, 180.1, 180.9. MS (EI, *m/z* (%)): 585 (M$^+$, 42), 584 (24), 325 (14), 270 (13), 155 (69), 154 (53), 127 (100), 104 (23), 77 (36). Anal. calcd. for $C_{33}H_{23}N_5O_6$: C, 67.69; H, 3.96; N, 11.96. Found: C, 67.39; H, 3.71; N, 11.61.

Ethyl 3-(3-acetyl-1-phenyl-1H-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**9c**): Color: Golden yellow crystals. Yield: 72% (MeCN). M.p.: 208-210 °C. FT-IR (KBr, cm^{-1}): 1714, 1693, 1662 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.22 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 2.5 (s, 3H, CH$_3$CO), 4.22 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 7.46-8.40 (m, 9H, Ar-H), 9.34 (s, 1H, =CH-N), 9.39 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 473 (M$^+$, 50), 386 (74), 372 (32), 213 (44), 171 (52), 103 (26), 77 (100). Anal. calcd. for $C_{24}H_{19}N_5O_6$: C, 60.89; H, 4.05; N, 14.79. Found: C, 60.52; H, 3.81; N, 14.41%.

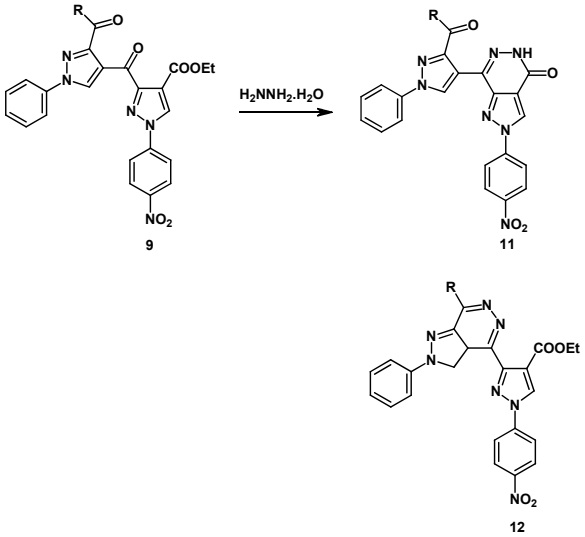
(E)-Ethyl 1-(4-nitrophenyl)-3-(1-phenyl-3-styryl-1H-pyrazole-4-carbonyl)-1H-pyrazole-4-carboxylate (**10a**): Color: Pale yellow crystals. Yield: 75% (MeCN). M.p.: 232-234 °C. FT-IR (KBr, cm^{-1}): 1710, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.17 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.30 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 7.41-8.41 (m, 16H, Ar-H, HC=CH), 9.0 (s, 1H, =CH-N), 9.6 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 533 (M$^+$, 67), 532 (56), 321 (56), 260 (28), 245 (31), 91 (25), 77 (100). Anal. calcd. for $C_{30}H_{23}N_5O_5$: C, 67.54; H, 4.35; N, 13.13. Found: C, 67.31; H, 4.21; N, 13.01%.

Ethyl 3-(3-(furan-2-yl)-1-(4-nitrophenyl)-1H-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylate (**10b**): Color: Brown crystals. Yield: 70% (EtOH). M.p.: 148-150 °C. FT-IR (KBr, cm^{-1}): 1715, 1671 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.16 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.19 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 6.68-8.40 (m, 11H, Ar-H), 9.34(s, 1H, =CH-N), 9.48 (s, 1H, =CH-N). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.8, 60.5, 111.7, 113.8, 116.1, 119.5, 119.6, 120.0, 120.9, 121.0, 121.3, 125.3, 133.4, 137.2, 142.7, 144.1, 145.7, 145.9, 152.4, 161.0, 181.2. MS (EI, *m/z* (%)): 542 (M$^+$, 93), 541 (45), 374 (15), 249 (17), 236 (64), 235 (48), 149 (15), 103 (56), 102 (46), 76 (100). Anal. calcd. for $C_{26}H_{18}N_6O_8$: C, 57.57; H, 3.34; N, 15.49. Found: C, 57.61; H, 3.21; N, 15.12%.

Ethyl 1-(4-nitrophenyl)-3-(1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carbonyl)-1H-pyrazole-4-carboxylate (**10c**): Color: Brown crystals. Yield: 71% (EtOH). M.p.: 236-238 °C. FT-IR (KBr, cm^{-1}): 1714, 1666 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.19 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$O), 4.22 (q, *J* = 7 Hz, 2H, CH$_3$C*H*$_2$O), 6.96-8.30 (m, 11H, Ar-H), 9.18 (s, 1H, =CH-N), 9.61 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 558 (M$^+$, 23), 557 (17), 409 (26), 308 (100), 111 (80), 93 (20). Anal. calcd. for $C_{26}H_{18}N_6O_7S$: C, 55.92; H, 3.25; N, 15.05;S, 5.73. Found: C, 55.71; H, 3.01; N, 14.79; S, 5.55%.

2.2.6. Synthesis of 2-(4-nitrophenyl)-7-(1-phenyl-3-substituted-1H-pyrazol-4-yl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-ones (11a-c, 13a-c)

General procedure: A mixture of the appropriate ethyl 3-(1-aryl-3-substituted-1*H*-pyrazole-4-carbonyl)-1-(4-nitrophenyl)-1*H*-pyrazole-4-carboxylate **9**(**10**) (3 mol) and hydrazine hydrate (5 mL, 99%) was refluxed for 3 h and then cooled. The solid that precipitated was collected, washed with hot ethanol and finally crystallized from the appropriate solvents. The compounds **11a-c** and **13a-c** prepared together with their physical constants are listed below (Scheme 4 and 5).

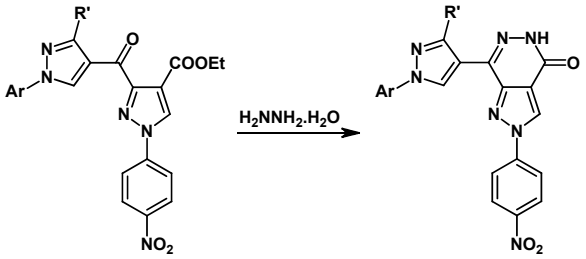


9(11)	R
a	C_6H_5
b	2-Naphthyl
c	CH_3

Scheme 4

7-(3-Benzoyl-1-phenyl-1H-pyrazol-4-yl)-2-(4-nitrophenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**11a**): Color: Yellow crystals. Yield: 82% (DMF). M.p.: 308-310 °C. FT-IR (KBr, cm^{-1}): 3242 ν(NH), 1695, 1670 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.51-8.25 (m, 14H, Ar-H), 9.22 (s, 1H, =CH-N), 9. 14 (s, 1H, =CH-N), 12.41 (s, 1H, NH). MS (EI, *m/z* (%)): 503 (M$^+$, 18), 502 (36), 367 (54), 311 (55), 252 (54), 154 (64), 153 (73), 105 (27), 104 (82), 103 (100). Anal. calcd. for $C_{27}H_{17}N_7O_4$: C, 64.41; H, 3.40; N, 19.47. Found: C, 64.13; H, 3.11; N, 19.11%.

7-(3-(2-Naphthoyl)-1-phenyl-1H-pyrazol-4-yl)-2-(4-nitro phenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**11b**): Color: Yellow crystals. Yield: 85% (DMF). M.p.: 302-304 °C. FT-IR (KBr, cm^{-1}): 3240 ν(NH), 1697, 1665 ν(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.40-8.24 (m, 15H, Ar-H), 8.70 (s, 1H, Ar-H), 9.16 (s, 1H, =CH-N), 9.55 (s, 1H, =CH-N), 12.41 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 116.4, 117.8, 119.5, 120.4, 120.6, 124.6, 124.7, 127, 127.6, 128.3, 129.0, 129.7, 1219.8, 132.0, 132.6, 133.1, 134.0, 135.2, 138.9, 142.7, 145.5, 146.2, 149.4, 157.5, 180.1. MS (EI, *m/z* (%)): 553 (M$^+$, 56), 552 (52), 380 (13), 277 (15), 276 (13), 127 (100), 77 (54). Anal. calcd. for $C_{31}H_{19}N_7O_4$: C, 67.27; H, 3.46; N, 17.71. Found: C, 67.31; H, 3.11; N, 17.55%.



10(13)	R'	Ar
a	$C_6H_5CH=CH$	C_6H_5
b	2-Furyl	4-NO_2-C_6H_4
c	2-Thienyl	4-NO_2-C_6H_4

Scheme 5

7-(3-Acetyl-1-phenyl-1H-pyrazol-4-yl)-2-(4-nitrophenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**11c**): Color: Pale yellow crystals. Yield: 81% (DMF). M.p.: 322-324 °C. FT-IR (KBr, cm^{-1}): 3255 ν(NH), 1700, 1670 ν(C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.4 (s, 3H, CH_3CO), 7.69-8.52 (m, 9H, Ar-H), 9.44 (s, 1H, =CH-N), 9.64 (s, 1H, =CH-N), 12.60 (s, 1H, NH). MS (EI, *m/z* (%)): 441 (M^+, 44), 440 (25), 398 (17), 397 (51), 142 (49), 104 (34), 77 (100). Anal. calcd. for $C_{22}H_{15}N_7O_4$: C, 59.86; H, 3.43; N, 22.21. Found: C, 59.81; H, 3.22; N, 22.01%.

(E)-2-(4-Nitrophenyl)-7-(1-phenyl-3-styryl-1H-pyrazol-4-yl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**13a**): Color: Colorless crystals. Yield: 79% (DMF). M.p.: 256-258 °C. FT-IR (KBr, cm^{-1}): 3359 ν(NH), 1688 ν(C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.41-8.41 (m, 17H, Ar-H, HC=CH, NH), 9.21 (s, 1H, =CH-N), 9.72 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 501 (M^+, 72), 500 (37), 424 (100), 378 (42), 250 (19), 77 (100). Anal. calcd. for $C_{28}H_{19}N_7O_3$: C, 67.06; H, 3.82; N, 19.55. Found: C, 66.99; H, 3.62; N, 19.77%.

7-(3-(Furan-2-yl)-1-(4-nitrophenyl)-1H-pyrazol-4-yl)-2-(4-nitrophenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**13b**): Color: Yellow crystals. Yield: 77% (DMF). M.p.: > 360 °C. FT-IR (KBr, cm^{-1}): 3280 ν(NH), 1692 ν(C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.6 (m, 1H, Ar-H), 7.11 (m, 1H, Ar-H), 8.27-8.46 (m, 10H, Ar-H, NH), 9.39 (s, 1H, =CH-N), 9.77 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 510 (M^+, 100), 509 (56), 481 (17), 388 (16), 373 (23), 255 (21), 217 (22), 195 (25), 103 (30), 76 (54). Anal. calcd. for $C_{24}H_{14}N_8O_6$ (510.43): C, 56.48; H, 2.76; N, 21.95. Found: C, 56.19; H, 2.51; N, 22.10%.

2-(4-Nitrophenyl)-7-(1-(4-nitrophenyl)-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (**13c**): Color: Pale yellow crystals. Yield: 80% (DMF). M.P.: 258-260 °C. FT-IR (KBr, cm^{-1}): 3348 ν(NH), 1686 ν(C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.82-8.23 (m, 12H, Ar-H, NH), 9.11 (s, 1H, =CH-N), 9.62 (s, 1H, =CH-N). MS (EI, *m/z* (%)): 526 (M^+, 100), 481 (76), 322 (38), 122 (38). Anal. calcd. for $C_{24}H_{14}N_8O_5S$ (526.43): C, 54.76; H, 2.68; N, 21.59; S, 6.08. Found: C, 54.44; H, 2.40; N, 21.81; S, 5.82%.

2.2.7. Synthesis of (E)-7-(2-(dimethylamino)vinyl)-2-(4-nitro phenyl)-2H-pyrazolo[3,4-d]pyridazin-4(5H)-one (14)

To a solution of 7-methyl-2-(4-nitrophenyl)-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one, **7a** (2.71 g, 0.01 mol) in dioxane (50 mL), was added dimethylformamide-dimethylacetal (1.2 g, 0.01 mol). The reaction mixture was refluxed for 10 h and then cooled to room temperature. The solid that was formed was filtered off and crystallized to give the enamine **14** (Scheme 6). Color: Pale yellow. Yield: 80% (DMF). M.p.: 278-280 °C. FT-IR (KBr, cm^{-1}): 3255 ν(NH), 1660 ν(C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 6H, $(CH_3)_2N$), 7.85-8.43 (m, 6H, Ar-H, HC=CH), 9.12 (s, 1H, =CH-N), 13.12 (s, 1H, NH). MS (EI, *m/z* (%)): 326 (M^+, 35), 326 (31), 271 (97), 270 (100), 240 (45), 214 (52), 114 (45), 172 (31), 121 (21), 110 (24), 89 (34). Anal. calcd. for $C_{15}H_{14}N_6O_3$: C, 55.21; H, 4.32; N, 25.75. Found: C, 55.01; H, 4.40; N, 25.55%.

2.2.8. Alternate synthesis of 11a and 13c

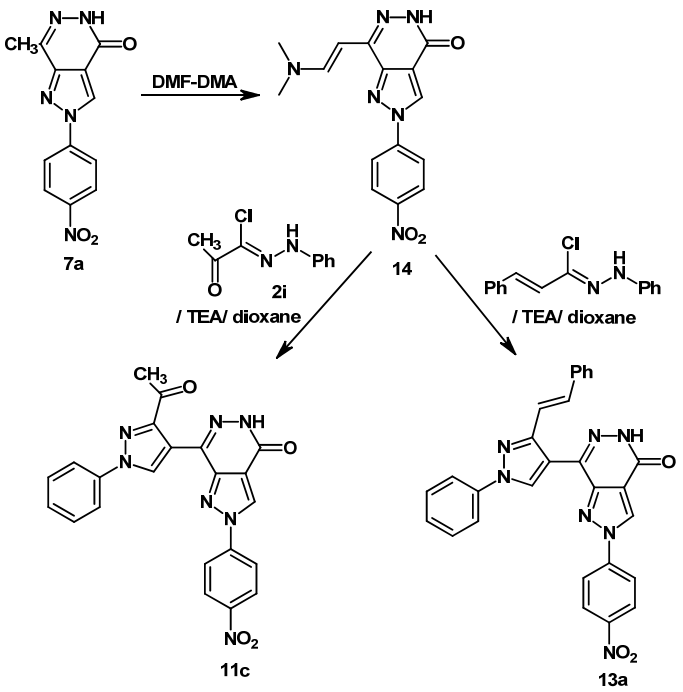
To an equimolar mixture of the enamine **14** and the hydrazonoyl chloride **2l** (5 mmol each) in dioxane (50 mL) was added triethylamine (0.6 g, 5 mmol) and the reaction mixture was refluxed for 8 h, then the solvent was distilled under reduced pressure. To the residue left was triturated with ethanol and the solid formed was collected and crystallized from DMF to give a product that proved identical in all respect (M.p., Mixed m.p., IR, ^1H NMR and elemental analysis) with **11c** obtained above from **9c** and hydrazine hydrate.When the above procedure was repeated using the hydrazonoyl chloride **3a** in lieu **2l**, the product obtained proved to be **13a** identical in all respect with that one obtained from reaction of **10a** with hydrazine hydrate.

3. Results and discussion

The target new enamino ester **1**, which has not been reported hitherto, was prepared in this study by reaction of dipropylamine with ethyl propiolate in methanol at room temperature (Scheme 1). Its structure was verified by elemental analysis and spectroscopic methods (IR and NMR) (see Experimental). For example, its ^1H NMR spectrum displayed a quartet and triplet signals at δ 1.15 and 4.02 due to the CH_3CH_2OCO group, two doublet signals at δ 4.42 and 7.36 with coupling constant J = 13 Hz assignable to the two olefinic protons. The latter coupling constant value indicates that the enamino ester prepared exists predominantly in the *E*-configuration. In addition to such signals, the ^1H NMR spectrum reveals three signals at δ 0.79 (6H), 1.47 (4H) and 2.97 (4H) assignable to the resonances of the protons of the $(CH_3CH_2CH_2)_2N$- moiety.

Next, the reactions of the enamino ester **1**, as a dipolarophile, with various nitrilimines, generated *in situ* by dehydrohalogenation of the respective *N*-aryl hydrazonoyl halides were examined. Thus, in our hands, reaction of compound **1** with each of compounds **2a-k** in refluxing dioxane in the presence of triethylamine yielded, in each case, a single product that was identified, on the basis of its elemental analysis and spectral (IR, NMR and MS) data as the corresponding ethyl 1-aryl-3-substituted-1*H*-pyrazole-4-carboxylate **4a-k** (Scheme 1).

Similar reactions of compound **1** with the halides **3a-d** under the same conditions afforded regioselectively the pyrazole derivatives **5a-d** (Scheme 1). The other possible regio-isomeric structure namely ethyl 1-aryl-3-substituted-1*H*-pyrazole-5-carboxylate **6** was discarded. This is because the ^1H NMR spectra of the products **4**(**5**) isolated showed in each case a singlet signal in the region δ 8.60– 9.22, which corresponds to H-5 of the pyrazole ring residue in the products. This assignment is consistent with literature reports which indicate that in pyrazole derivatives, the signal of H-5 usually appears at δ 8.66-8.69 whereas that of H-4 appears at δ 5.81-5.89 [25]. The formation of compounds **4**(**5**) rather than compound **6** indicates that the studied reaction of compound **1** with compounds **2**(**3**) is regiospecific. To account for the formation of compounds **4**(**5**), it is suggested, as depicted in Scheme 1 that the reaction of compound **1** with each of compounds **2** and **3** proceeds *via* 1,3-dipolar cycloaddition of the nitrilimine, derived from compounds **2**(**3**), to the activated double bond in the enamino ester, **1**, to give the respective cycloadducts which in turn undergo *in situ* elimination of dipropylamine to afford compounds **4**(**5**) as the end products.



Scheme 6

The assigned structures **4** for the isolated products were further confirmed by their chemical reactions. For example, treatment of compounds **4a-k** each with hydrazine hydrate in refluxing ethanol yielded in each case one product whose spectroscopic (MS, IR, NMR) and elemental analysis data were consistent with the structure of the corresponding 2-aryl-7-substituted-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one, **7a-k** (Scheme 2).

Condensation of the pyrazole derivative **4a** with DMF-DMA in refluxing dioxane afforded the corresponding enaminone, **8** (Scheme 3). The structure of the latter enaminone was confirmed by its spectral and elemental analyses. For example, its IR spectrum showed C=O bands at ν 1700 and 1647 cm^{-1}. Its ^{1}H NMR spectrum revealed a singlet signal at δ 3.14 (6H) for the protons of the $(CH_3)_2N$- group, two characteristic doublets at δ 6.27 (d, 1H) and 8.76 (d, 1H) with coupling constant J = 13 Hz assignable to the two olefinic protons. This coupling constant value indicates that this enaminone, **8**, has the indicated *trans*-configuration.

Similar to the enamino ester **1**, the enaminone, **8**, reacted with various hydrazonoyl halides **2e**, **2h**, **2l** and **3a-c** in refluxing dioxane in the presence of triethylamine and yielded the corresponding *bis*-3,4'-pyrazolyl ketones, **9a-c** and **10a-c** (Scheme 3). The structures of the latter products were established by their spectral and elemental analysis data (see Experimental).

Next, hydrazinolysis of the products **9** was studied to shed some light on its site selectivity as it can theoretically lead to the formation of the products **11** and/or **12** (Scheme 4). When each of compounds **9** was refluxed with hydrazine hydrate in ethanol, it yielded chemoselectively a single product in each case as evidenced by TLC analysis of the crude product. The isolated products proved to be the corresponding 2-(4-nitrophenyl)-7-(3-aroyl-1-phenyl-1*H*-pyrazol-4-yl)-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one, **11**, (Scheme 4). The structures of the latter products **11** were established on the basis of their spectral and elemental analysis data (see Experimental). For example, the IR spectra of products **11** revealed two C=O bands near ν 1697 and 1665 cm^{-1} in addition to NH band at ν 3240 cm^{-1}. Their ^{1}H NMR spectra revealed the absence of the triplet and quartet signals characteristic of the ester group, -$COOCH_2CH_3$.

Similar treatment of compounds **10** with hydrazine hydrate in refluxing ethanol afforded the corresponding 2-(4-nitrophenyl)-7-(1-phenyl-3-substituted-1*H*-pyrazol-4-yl)-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-one, **13** (Scheme 5). The structures of the latter products were established by their spectral and elemental analysis data (see Experimental).

To provide further evidence for the assigned structures of the products **11** and **13**, they were prepared by an unambiguous alternate synthesis (Scheme 6). Thus, treatment of compound **7a** with DMF-DMA in dioxane yielded the corresponding enamine**14**. Reaction of the latter with each of the hydrazonoyl chlorides **2l** and **3a** in dioxane in the presence of triethylamine afforded two products that proved identical in all respects with compounds **11c** and **13a**, prepared from hydrazinolysis of compounds **9c** and **10a**, respectively (Scheme 4 and 5).

4. Conclusion

In summary, ethyl 3-(dipropylamino)acrylate and C-acyl nitrilimines proved useful precursors for synthesis of 3,4-*bis*-(functionalized carbonyl) derivatives of pyrazole **4** and 3,4'-*bis*-(pyrazolyl) ketones, **9**(**10**). In addition, reaction of **4** with hydrazine hydrate afforded the corresponding pyrazolo[3,4-*d*]pyridazin-4(5)-ones, **7**. Similar hydrazinolysis of **9**(**10**) proved to be site selective as it yielded the corresponding 7-substituted-2*H*-pyrazolo[3,4-*d*]pyridazin-4(5)-ones, **11**(**13**).

References

[1]. Shawali, A. S.; Parkanyi, C. *J. Heterocycl. Chem.* **1980**, *17*, 833-854.
[2]. Shawali, A. S. *Heterocycles* **1983**, *20*, 2239-2285.
[3]. Shawali, A. S. *Chem. Rev.* **1993**, *93*, 2731-2777.
[4]. Shawali, A. S.; Abdallah, M. A. *Adv. Heterocycl. Chem.* **1995**, *63*, 277-338.
[5]. Shawali, A. S.; Elsheikh, S. M. *J. Heterocycl. Chem.* **2001**, *38*, 541-559.

[6]. Shawali, A. S.; Mosselhi, M. A. N. *J. Heterocycl. Chem.* **2003**, *40*, 725-746.
[7]. Shawali, A. S.; Mosselhi, M. A. N. *J. Sulfur. Chem.* **2005**, *26*, 267-303.
[8]. Shawali, A. S.; Edrees, M. M. *Arkivoc* **2006**, *9*, 292-365.
[9]. Shawali, A. S.; Sherif, S. M. *Current Org. Chem.* **2007**, *11*, 773-799.
[10]. Osterloh, J. H.; *Birkhauser Verlag Basel* **2004**, 1-13.
[11]. Rainer, G.; Kruger, U.; Klemm K. *Arzneimittel-Forschung* **1981**, *31*, 649-655.
[12]. Goertz, R.; Appelboom, T. *Int. J. Tissue React.* **1985**, *7*, 263-265.
[13]. Vinge, E.; Bjorkman, S. B. *ActaPharmacol. Toxicol* **1986**, *59*, 165-174.
[14]. Kameyama, T.; Ukai, M.; Nabeshima, T. *Chem. Pharm. Bull.* **1978**, *26*, 3265-3270.
[15]. Akbas, E.; Berber, I. *Eur. J. Med. Chem.* **2005**, *40*, 401-405.
[16]. Bildirici, I.; Sener, A.; Tozlu, J. *Med. Chem. J.* **2007**, *16*, 418-426.
[17]. Bildirici, I.; Sener, A.; Battal, A. *Med. Chem. J.* **2009**, *18*, 327-340.
[18]. Eweiss, N. F.; Osman, A. *J. Heterocycl. Chem.* **1980**, *11*, 1713-1717.
[19]. Hassaneen, H. M.; Mousa, H. A. H.; Abed, N. M.; Shawali, A. S. *Heterocycles* **1988**, *27*, 695-706.
[20]. Shawali, A. S.; Hassaneen, H. M.; Ibrahim, H. A.; Mekki, S. T.; Fahmi, A. A. *Arch. Pharm. Res.* **1990**, *13*, 126-131.
[21]. Hassaneen, H. M.; Hilal, R. H.; Elwan, N. M.; Harhash, A.; Shawali, A. S. *J. Heterocycl. Chem.* **1984**, *21*, 1013-1016.
[22]. Farag, A. M.; Algharib, M. S. *Org. Prep. Proc. Int.* **1988**, *20*, 521-526.
[23]. Shawali, A. S.; Abdelhamid, A. O. *Bull. Chem. Soc. Japan* **1976**, *49*, 321-332.
[24]. Shawali, A. S.; Eweiss, N. F.; Hassaneen, H. M.; Sami, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 365-366.
[25]. Shawali, A. S.; Farghaly, T. A.; Al-Dahshoury, A. R. *Arkivoc* **2009**, *14*, 88-99.