

Reactions with Hydrazonoyl Halides. 31. Synthesis of Some New Pyrrolidino[3,4-*c*]pyrazolines, Pyrazoles, and Pyrazolo[3,4-*d*]pyridazines[†]

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[†] For part 30 see [1].

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Abstract: Pyrrolidino[3,4-*c*]pyrazoline and pyrazole derivatives were synthesized via reactions of a substituted hydrazonoyl bromide with *N*-arylmaleimides and active methylene reagents, respectively. Synthesized pyrazoles were reacted with hydrazine hydrate to give the corresponding pyrazolo[3,4-*d*]pyridazines.

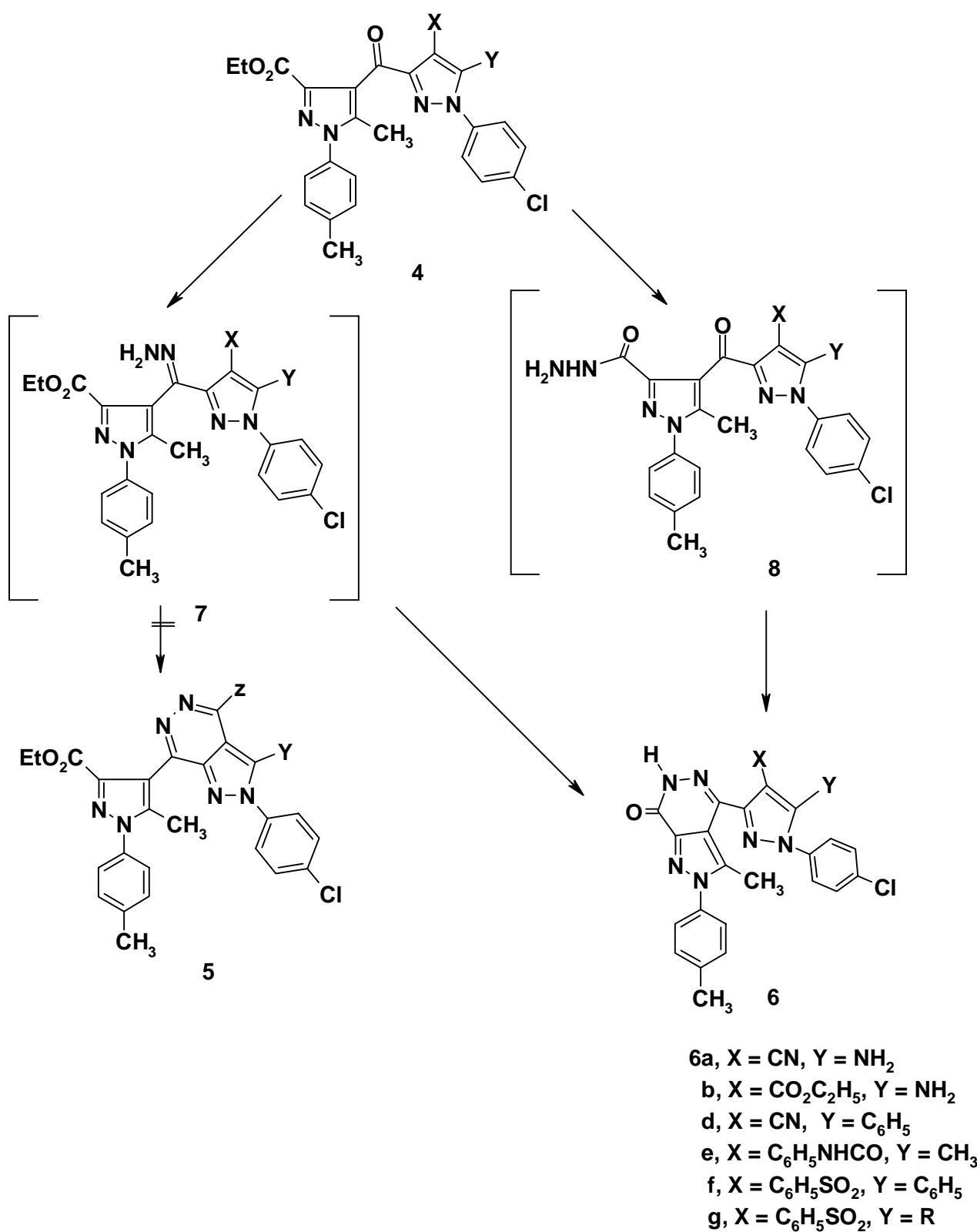
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Introduction

Hydrazonoyl halides have been widely employed in the synthesis of heterocyclic derivatives [2-5]. In continuation of our interest in the synthesis of heterocyclic systems containing a pyrazole moiety [6-10], we report herein a facile synthesis of pyrrolidino[3,4-*c*]pyrazoline, pyrazole, and pyrazolo[3,4-*d*]pyridazine derivatives.

Results and Discussion

Treatment of the hydrazonoyl bromide **1** [10] with the appropriate *N*-arylmaleimides **2a-c** in benzene containing triethylamine afforded pyrrolidino[3,4-*d*]pyrazolines **3a-c** (cf. Scheme 1). The structures of compounds **3a-c** were confirmed by their spectroscopic data. For example, the ¹H NMR spectrum of **3a**



Scheme 2.

Experimental

General

All melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ¹H NMR spectra were recorded in CDCl₃ on a Varian Gemini 200 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. Hydrazonoyl bromides **1** [10] and *N*-arylmaleimides **2a-c** [12] were prepared as previously reported.

General procedure for the synthesis of 5-aryl-1-(4-chlorophenyl)-3-[3'-ethoxycarbonyl-5'-methyl-1'-(4-tolyl)-4'-pyrazoloyl]pyrrolidino[3,4-*c*]pyrazoline-4,6-diones (**3a-c**)

A solution of the substituted hydrazonoyl bromide **1** (2.5 g, 0.005 mol), the appropriate *N*-arylmaleimides **2a-c** (0.005 mol) and triethylamine (0.7 mL, 0.005 mol) in dry benzene (20 mL) was refluxed for 3 h. The solvent was removed under vacuum and the residue triturated with petroleum ether (b.p. 40/60°C, 10 mL). The resulting solid was collected, washed and crystallized from acetic acid or ethanol to give **3a-c** (cf. Table 1).

General procedure for the synthesis of 4,5-disubstituted 1-(4-chlorophenyl)-3-[3'-ethoxy-carbonyl-5'-methyl-1'-(4-tolyl)-4'-pyrazoloyl]pyrazoles (**4a-g**)

The appropriate active methylene compound (malononitrile, ethyl cyanoacetate dibenzoylmethane, benzoylacetonitrile, acetoacetanilide, ω-benzenesulfonylacetophenone, or ketosulfone. (0.005 mol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (0.11 g-atom) in absolute ethanol (20 mL)]. After stirring for 10 minutes, the hydrazonoyl bromide **1** (2.5 g, 0.005 mol) was added and stirring was continued for an additional 30 minutes. The reaction mixture was left overnight at room temperature and the precipitated product was collected by filtration. The solid was washed with water and recrystallized from ethanol to give the corresponding pyrazoles **4a-g**, respectively (cf. Table 1).

General procedure for the synthesis of 4,5-disubstituted 4-[1-(4-chlorophenyl)-3-pyrazolyl]-2,6-dihydro-3-methyl-2-(4-tolyl)-pyrazolo[3,4-*d*]pyridazin-7-ones (**6a,b,d-g**)

The appropriate pyrazoles (**4a,b** and **4d-g**) (0.005 mol) in a mixture of ethanol (20 mL) and hydrazine hydrate (0.75 mL, 0.015 mol) were refluxed for 4h, during which time the pyrazole dissolved and the corresponding pyrazolo[3,4-*d*]pyridazine precipitated. The latter was collected, washed with water and recrystallized from ethanol or dimethylformamide to give **6a,b,d-g** (cf. Table 1).

Table 1. Analytical data of the newly synthesized compounds.

Compd no.	Color	Yield %	M.P., °C Solvent	Mol.Formula Mol.Wt.	% Analyses, Calcd. /Found			
					C	H	N	S
3a	Yellowish green	77	250-253	C ₃₂ H ₂₆ ClN ₅ O ₅	64.48	4.40	11.75	
			EtOH	596.05	64.70	4.30	11.60	
3b	Yellowish green	78	228-230	C ₃₃ H ₂₈ ClN ₅ O ₅	64.97	4.63	11.48	
			EtOH	610.07	65.10	4.50	11.30	
3c	Yellowish green	82	285-287	C ₃₃ H ₂₈ ClN ₅ O ₆	63.31	4.51	11.19	
			AcOH	626.07	63.10	4.50	11.00	
4a	Yellow	85	208-10	C ₂₅ H ₂₁ ClN ₆ O ₃	61.41	4.33	17.19	
			EtOH	488.94	61.22	4.20	17.30	
4b	Colorless	80	243-245	C ₂₇ H ₂₆ ClN ₅ O ₅	60.50	4.89	13.07	
			EtOH	535.99	60.60	4.90	12.90	
4c	Yellow	92	197-200	C ₃₇ H ₂₉ ClN ₄ O ₄	70.64	4.65	8.91	
			EtOH	629.12	70.60	4.40	8.80	
4d	Yellow	76	185-187	C ₃₁ H ₂₄ ClN ₅ O ₃	67.70	4.40	12.73	
			EtOH	550.02	67.90	4.30	12.80	
4e	Yellow	69	175-178	C ₃₂ H ₂₈ ClN ₅ O ₄	66.03	4.85	12.03	
			EtOH	582.06	66.10	5.00	11.90	
4f	Yellow	82	127-130	C ₃₆ H ₂₉ ClN ₄ O ₅ S	65.01	4.39	8.42	4.82
			EtOH	665.17	65.20	4.10	8.20	4.90
4g	Brown	78	140-143	C ₄₄ H ₃₉ ClN ₆ O ₇ S	63.57	4.73	10.11	3.86
			EtOH	831.35	63.40	4.73	10.20	3.70
6a	Orange	72	200-203	C ₂₃ H ₁₇ ClN ₈ O	60.46	3.75	24.52	
			EtOH	456.90	60.20	3.90	24.70	
6b	Yellow	62	227-230	C ₂₂ H ₂₂ ClN ₇ O ₃	59.58	4.40	19.46	
			EtOH	503.95	59.50	4.40	19.60	
6d	Colourless	70	310-12	C ₂₉ H ₂₀ ClN ₇ O	67.25	3.89	18.93	
			EtOH	517.98	67.30	4.10	18.80	
6e	Colourless	66	307-10	C ₃₀ H ₂₄ ClN ₇ O ₂	65.51	4.40	17.83	
			EtOH	550.02	65.50	4.50	17.90	
6f	Yellow	73	197-200	C ₃₄ H ₂₅ ClN ₆ O ₃ S	64.50	3.98	13.27	5.60
			EtOH	633.13	64.40	4.20	13.40	5.40
6g	Yellow	78	320-22	C ₄₂ H ₃₅ ClN ₈ O ₅ S	63.11	4.41	14.02	4.44
			EtOH	799.31	63.30	4.20	14.20	4.30

Table 2. IR and ¹H-NMR spectroscopic data.

Comp no.	IR (cm ⁻¹)	¹ H NMR (δ ppm)
3a	1740-1720 and 1710-1690 (CO's)	1.11 (t, 3H, <u>CH₂CH₃</u>); 2.33 (s, 3H, CH ₃); 2.41 (s, 3H, CH ₃); 4.12 (q, 2H, <u>CH₂CH₃</u>); 5.20 (d, 1H, pyrazoline H-4); 5.49 (d, 1H, pyrazoline H-5) and 7.16-7.46 (m, 13H, ArH).
3b	1740-1720 and 1710-1690 (CO's)	1.11 (t, 3H, <u>CH₂CH₃</u>); 2.33 (s, 3H, CH ₃); 2.41 (s, 6H, 2CH ₃); 4.12 (q, 2H, <u>CH₂CH₃</u>); 5.02 (d, 1H, pyrazoline H-4); 5.49 (d, 1H, pyrazoline H-5) and 7.14-7.46 (m, 12H, ArH).
3c	1740-1720 and 1710-1690 (CO's)	1.11 (t, 3H, <u>CH₂CH₃</u>); 2.33 (s, 3H, CH ₃); 2.41 (s, 3H, CH ₃); 4.92 (s, 3H, OCH ₃); 4.12 (q, 2H, <u>CH₂CH₃</u>); 5.02 (d, 1H, pyrazoline H-4); 5.49 (d, 1H, pyrazoline H-5) and 7.14-7.46 (m, 12H, ArH).
4a	3292,3176 (NH ₂); 2229 (CN); 737, 1659 (CO's).	1.02 (t, 3H, <u>CH₂CH₃</u>); 2.40 (s, 3H, CH ₃); 2.43 (s, 3H, CH ₃); 4.01 (q, 2H, <u>CH₂CH₃</u>); 7.14 (s, br., 2H, NH ₂) and 7.37-7.68 (m, 8H, ArH's).
4b	3272, 3185 (NH ₂), 1730, 1647 (CO's).	1.02 (t, 3H, <u>CH₂CH₃</u>); 1.10 (t, 3H, <u>CH₂CH₃</u>); 2.40 (s, 3H, CH ₃); 2.43 (s, 3H, CH ₃); 4.01 (q, 2H, <u>CH₂CH₃</u>); 4.21 (q, 2H, <u>CH₂CH₃</u>); 7.14 (s, br., 2H, NH ₂) and 7.37-7.68 (m, 8H, ArH).
4c	1720, 1685, 1660 (CO's)	1.23 (t, 3H, <u>CH₂CH₃</u>); 2.32 (s, 3H, CH ₃); 2.39 (s, 3H, CH ₃); 4.24 (q, 2H, <u>CH₂CH₃</u>); 7.19-8.09 (m, 18H, ArH).
4d	2236 (CN); 1724, 1658 (CO's).	1.07 (t, 3H, <u>CH₂CH₃</u>); 2.42 (s, 3H, CH ₃); 2.49 (s, 3H, CH ₃); 4.13 (q, 2H, <u>CH₂CH₃</u>); and 7.17-7.50 (m, 13H, ArH).
4e	3240 (NH); 1735, 1668 (CO's).	1.05 (t, 3H, <u>CH₂CH₃</u>); 2.41 (s, 3H, CH ₃); 2.50 (s, 3H, CH ₃); 2.75 (s, 3H, CH ₃); 4.03 (q, 2H, <u>CH₂CH₃</u>); 7.32-7.88 (m, 13H, ArH) and 11.64 (s, br., 1H, NH).
4f	1730,1667 (CO's); 1314,1140 (SO ₂).	1.05 (t, 3H, <u>CH₂CH₃</u>); 2.34 (s, 3H, CH ₃); 2.44 (s, 3H, CH ₃); 4.03 (q, 2H, <u>CH₂CH₃</u>); and 7.32-7.88 (m, 18H, ArH).
4g	1730, 1667 (CO's) and 1314, 1140 (SO ₂).	1.04 (t, 3H, <u>CH₂CH₃</u>); 1.14 (t, 3H, <u>CH₂CH₃</u>); 2.39 (s, 6H, 2CH ₃); 2.43 (s, 6H, CH ₃); 4.02 (q, 2H, <u>CH₂CH₃</u>); 4.12 (q, 2H, <u>CH₂CH₃</u>) and 7.26-8.04 (m, 17H, ArH).
6a	3340, 3292, 3176 (NH ₂ , NH); 2220 (CN); 1668 (CO)	2.43 (s, 3H, CH ₃); 2.55 (s, 3H, CH ₃); 6.90 (s, 2H, NH ₂); 7.04-7.65 (m, 8H, ArH) and 11.63 (s, 1H, NH).
6b	3244 (NH); 1710, 1666 (CO).	1.33 (t, 3H, <u>CH₂CH₃</u>); 2.39 (s, 3H, CH ₃); 2.67 (s, 3H, CH ₃); 4.12 (q, 2H, <u>CH₂CH₃</u>); 6.22 (s, 2H, NH ₂) and 7.00-7.79 (m, 8 H, ArH); 10.62 (s, 1H, NH).
6d	3345 (NH); 2233 (CN); 1674 (CO).	2.40 (s, 3H, CH ₃); 2.67 (s, 3H, CH ₃); 7.21-7.73 (m, 13H, ArH) and 12.65 (s, 1H, NH).
6e	3244 (NH); 1666 (CO)	2.39(s, 3H, CH ₃); 2.67(s, 3H, CH ₃); 2.42(s, 3H, CH ₃); 7.00-7.79(m, 13H, ArH); 10.62(s, 1H, NH) and 102.35(s, 1H, NH)
6f	3222 (NH); 1663 (CO); 1314, 1140 (SO ₂).	2.34 (s, 3H, CH ₃); 2.44 (s, 3H, CH ₃); 7.13-7.54 (m, 18H, ArH) and 10.33 (s, 1H, NH).
6g	3222 (NH); 1663 (CO); 1314, 1140 (SO ₂).	Insoluble

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Sample Availability: Available from MDPI.