A New Synthesis of Pyrazolo[1,5-*c*]pyrimidines from Acetylenic β-Diketones[1)]

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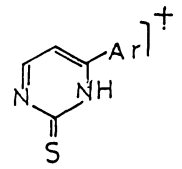
5-Aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones have been synthesized by the reaction of 1,5-diaryl-4-pentyne-1,3-diones with thiosemicarbazide and their reactions were studied. The pyrazolopyrimidinethiones give with certain electrophiles the respective 3-substituted 7-thiones. Their oxidation affords the corresponding disulfide. Moreover, they can be converted to the corresponding pyrazolopyrimidinones on reaction with alkaline hydrogen peroxide. The structure of the above compounds was confirmed from their spectral characteristics.

Pyrazolo[1,5-*c*]pyrimidines represent a biologically important class of compounds. Several of their derivatives are known to possess significant hypnotic, tranquilizing,[2)] fungicidal, insecticidal,[3)] and antibacterial[4)] activities. They are generally synthesized by the reaction of pyrylium salts,[5)] triketones[2,6)] or isothiocyanates[7)] with hydrazine derivatives.

In the present study, a new series of 5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (**2a**—**c**) were synthesized from the reaction of the respective 1,5-diaryl-4-pentyne-1,3-diones **1a**—**c** with thiosemicarbazide in refluxing ethanol (Scheme 1). This reaction provides a new synthesis of pyrazolo[1,5-*c*]pyrimidinethiones carrying aryl substituents of which only a few examples are reported in the literature.[4)]

The infrared spectra of **2** showed characteristic pyrazole and pyrimidine ring bands at 1570—1640 and 1520—1545 cm^{-1} as well as a thiocarbonyl and NH absorptions (cf. Experimental). It is worthy to note that the lack of ν_{SH} absorption in their spectra indicates that in the solid state the thione form predominates over the enethiol one. Their electronic spectra in neutral and in acidic solutions were similar; however, in basic medium a different pattern was observed (Table 1).

The ^1H NMR spectra of **2** (Table 2), showed two singlets at δ=7.03—7.10 and 7.13—7.23 for the H-3 and H-4 ring protons. Moreover, besides the NH proton, in the case of **2b**,**c** a singlet at δ=4.00—4.43 was observed, which may suggest some contribution of the thiol form. Further support of the structure of the



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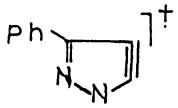

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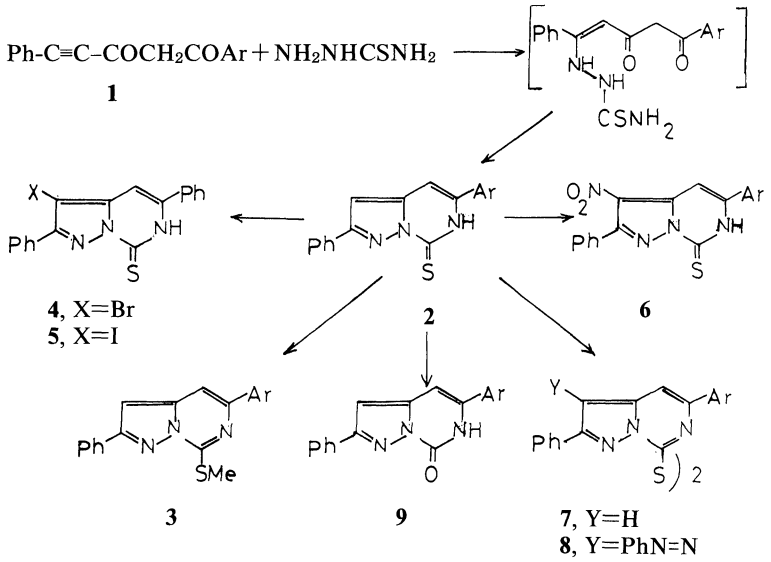

Ar: **a**=Ph, **b**=*p*-Me-C_6H_4, **c**=*p*-MeO-C_6H_4.

Scheme 1.

Table 1. Electronic Spectra of Pyrazolopyrimidine Derivatives

Compd	Solvent	λ_{max}/nm	(ε)
2a	Methanol	259, 294, 330	(45955, 32825, 17170)
	0.1 M $NaOCH_3$[b]	270, 332	(50500, 16160)
2b	Methanol	260, 294, 334	(46124, 25677, 17118)
	0.1 M $NaOCH_3$	266, 330	(63400, 17752)
2c	Methanol	266, 286, 332	(43290, 42180, 20350)
	0.1 M $NaOCH_3$	272, 332	(67155, 20350)
3a	Methanol	268, 318	(72834, 24530)
3b	Methanol	270, 319	(60153, 21961)
3c	Methanol	274, 320	(44952, 25631)
4	Methanol[a]	276, 320	
5	Methanol[a]	272, 312	
6a	Chloroform	280, 406	(41842, 12636)
6b	Chloroform[a]	280, 410	
6c	Chloroform	280, 400	(29747, 14380)
7a	Methanol[a]	272, 316, 430	
7b	Methanol[a]	272, 332, 406	
7c	Methanol[a]	283, 327, 411	
8a	Methanol	270, 320	(73080, 29435)
	0.1 M H_2SO_4	271, 322, 512	(69020, 28623, 2030)
8b	Methanol	260, 324	(101250, 42750)
	0.1 M H_2SO_4	259, 320, 520	(102000, 45375, 7500)
8c	Methanol	276, 318	(54046, 34517)
	0.1 M H_2SO_4	280, 320, 512	(52229, 37242, 4996)
9a	Methanol	250, 307	(32288, 24395)
	0.1 M $NaOCH_3$	250, 330	(56539, 24933)
9b	Methanol	248, 308	(40491, 30817)
	0.1 M $NaOCH_3$	250, 328	(58050, 26517)
9c	Methanol	256, 314	(40314, 35146)
	0.1 M $NaOCH_3$	258, 328	(59610, 29977)

a) Saturated solution. b) 1 M=1 mol dm^{-3}.

Table 2. ^1H NMR Spectral Data of Pyrazolopyrimidine Derivatives[a]

Compd	Solvent	Chemical shifts (δ/ppm)			
		H_3 and H_4 (s, 2H)	NH[c] (s, 1H)	ArH (m)	Others (s)
2a	DMSO-d_6	7.10, 7.23	13.20	7.80	
2b	DMSO-d_6	7.07, 7.13	12.97	7.76	2.33 (3H, CH_3), 4.43 (SH)[c]
2c	DMSO-d_6	7.03, 7.13	13.13	7.58	3.90 (3H, OCH_3), 4.00 (SH)[c]
3a	$CDCl_3$	6.64 (a)		7.62	2.74 (3H, SCH_3)
3b	$CDCl_3$	6.17, 6.67		7.51	2.37 (3H, CH_3), 2.77 (3H, SCH_3)
3c	$CDCl_3$	6.76, 6.94		7.55	3.93 (3H, OCH_3), 2.87 (3H, SCH_3)
4	C_5D_5N	7.07		7.77	
5	C_5D_5N	7.00		7.68	
7a	CF_3COOD	b)		7.99	
7b	CF_3COOD	b)		7.99	2.23 (3H, CH_3)
7c	CF_3COOD	b)		7.77	4.05 (3H, OCH_3)
8a	$CDCl_3$	b)		7.40	
8b	$CDCl_3$	b)		7.64	2.36 (6H, $2CH_3$)
8c	$CDCl_3$	b)		7.40	3.79 (6H, $2OCH_3$)
9a	DMSO-d_6	7.20, 7.34		7.82	
9b	DMSO-d_6	6.73, 6.80	11.38	7.52	2.30 (3H, CH_3)
9c	DMSO-d_6	6.70, 6.83		7.49	3.78 (3H, OCH_3)

a) s: Singlet. m: Multiplet. b) The H-3 and/or H-4 signals are overlapped by the aromatic protons multiplet. c) Exchangeable with D_2O.

pyrazolopyrimidinethiones was obtained from their mass spectra (cf. Experimental). These compounds gave their molecular ions as the base or very intense peaks. The detection of the pyrimidine radical cation **i** and the pyrazolyne species **ii** characterizes their spectra.

Methylation of **2a**—**c** with methyl iodide in the presence of anhydrous potassium carbonate afforded the 7-methylthio derivatives **3a**—**c** in excellent yield (Scheme 1). The chemical shift of the SCH_3 protons in the ^1H NMR spectra of **3** (Table 2), appears almost in the

Table 3. Analytical Data of Pyrazolopyrimidine Derivatives

Compd	Mp	Yield	Formula	Calcd/%					Found/%				
	°C	%		C	H	N	S	X	C	H	N	S	X
2a	236—238	65	$C_{18}H_{13}N_3S$	71.3	4.3	13.9	10.6		71.6	4.3	13.6	10.3	
2b	268—270	58	$C_{19}H_{15}N_3S$	71.9	4.7	13.2	10.1		71.5	4.4	13.0	9.8	
2c	284—287	75	$C_{19}H_{15}N_3OS$	68.5	4.5	12.6	9.6		68.8	4.2	12.8	9.3	
3a	132—136	83	$C_{19}H_{15}N_3S$	71.9	4.7	13.2	10.1		71.6	4.9	13.5	9.8	
3b	168—170	96	$C_{20}H_{17}N_3S$	72.5	5.1	12.7	9.7		72.8	5.3	12.4	9.7	
3c	167—169	96	$C_{20}H_{17}N_3OS$	69.2	4.9	12.1	9.2		69.5	5.2	12.4	9.4	
4	234—236	80	$C_{18}H_{12}BrN_3S$	56.5	3.1	10.9	8.4	20.9	56.2	2.8	10.6	8.7	21.2
5	262—264	90	$C_{18}H_{12}IN_3S$	50.3	2.8	9.8	7.5	29.6	50.7	2.4	9.6	7.2	30.0
6a	273—275	87	$C_{18}H_{12}N_4O_2S$	62.1	3.4	16.1	9.2		61.8	3.1	16.4	9.5	
6b	285—288	75	$C_{19}H_{14}N_4O_2S$	62.9	3.9	15.5	8.8		62.6	4.1	15.1	9.1	
6c	230—233	90	$C_{19}H_{14}N_4O_3S$	60.3	3.7	14.8	8.5		59.9	3.3	14.5	8.8	
7a	282—285	35	$C_{36}H_{24}N_6S_2$	71.5	3.9	13.9	10.9		71.1	3.5	13.6	10.6	
7b	293—295	38	$C_{38}H_{28}N_6S_2$	72.2	4.4	13.3	10.1		72.5	4.1	13.0	10.4	
7c	268—270	45	$C_{38}H_{28}N_6O_2S_2$	68.7	4.2	12.7	9.6		68.4	4.5	12.3	9.9	
8a	108—110	45	$C_{48}H_{32}N_{10}S_2$	70.9	3.9	17.2	27.9		70.6	3.7	16.8	7.6	
8b	190—195	48	$C_{50}H_{36}N_{10}S_2$	71.4	4.3	16.7	7.6		71.3	4.0	16.3	7.2	
8c	93—95	50	$C_{50}H_{36}N_{10}O_2S$	68.8	4.1	16.1	7.3		68.4	3.9	16.4	7.0	
9a	304—306	87	$C_{18}H_{13}N_3O$	75.3	4.5	14.6			75.6	4.7	14.9		
9b	325—328	90	$C_{19}H_{15}N_3O$	75.7	4.9	13.9			75.9	5.0	13.6		
9c	288—290	80	$C_{19}H_{15}N_3O_2$	71.9	4.7	13.2			72.1	4.9	13.0		

same range assigned to the SCH_3 protons in several 4,6-diaryl-2-methylthiopyrimidines.[8,9] Moreover, their H-3 and H-4 protons resonate at lower field ($\Delta\delta$=0.27—0.90 ppm) relative to the parent thiones **2**.

No reports on the electrophilic substitution reactions of pyrazolo[1,5-*c*]pyrimidinethiones have been made earlier. However, bromination,[10,11] iodination,[12,13] and nitration[11] of pyrazolo[1,5-*a*]pyrimidines generally lead to the formation of their 3- or 3,6-disubstituted derivatives. In the present work, bromination of **2a** with bromine as well as iodination with iodine monochloride gave the respective 3-bromo **4** and 3-iodo **5** derivatives. Moreover, nitration of **2a**—**c** with nitric and sulfuric acids in glacial acetic acid led to the formation of the corresponding 3-nitro **6a**—**c** derivatives (Scheme 1, Tables 1—3). It is worthy to note that the detection of the nitropyrazole species at *m/z* 187 in the mass spectrum of **6a**, while no nitropyrimidine fragment appeared supports the introduction of the nitro group at position 3 in the parent pyrazolopyrimidinethiones.

Oxidation of the pyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (**2a**—**c**) with sodium nitrite in glacial acetic acid afforded the corresponding 7,7′-dithiobis[5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine] **7a**—**c** (Scheme 1). While direct introduction of an arylazo group into the pyrazolopyrimidine ring system has not been reported, treatment of **2a**—**c** with benzenediazonium chloride in the presence of sodium hydroxide gave the 3-phenylazo derivatives **8a**—**c**. The reaction is assumed to proceed by introduction of phenylazo group as well as oxidation of the thiol. Their IR and ^1H NMR spectra gave characteristic bands (cf. Experimental and Table 2).

While 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine underwent rearrangement with alkaline hydrogen peroxide to give 6-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol,[14] the reaction of the pyrazolo[1,5-*c*]pyrimidinethiones (**2a**—**c**) with the same reagent led to the formation of the respective pyrazolo[1,5-*c*]pyrimidin-7(6*H*)-ones (**9a**—**c**) in excellent yield (Scheme 1). The presence of a broad OH absorption in the IR spectra of **9** suggests that in the solid state a significant contribution of the enol form occurs.

Experimental

General Methods. Microanalyses were performed by the Microanalysis Unit, Cairo University, Cairo. IR spectra were measured with a Unicam SP 1025 spectrophotometer for potassium bromide pellets and electronic spectra were measured with a Unicam SP 800 spectrophotometer. The ^1H NMR spectra were recorded on a Varian EM-390 NMR spectrometer at 90 MHz with TMS as internal standard. Mass spectra were recorded at 70 eV with an AEL MS-9 spectrometer coupled to a DS-50 Data system using a direct insertion probe for introduction of samples. TLC were done on Merck kieselgel 60-F 254 precoated plastic plates.

5-Aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (2). (Tables 1—3). A solution of 1,5-diaryl-4-pentyne-1,3-dione[15] **1a**—**c** (1.9 mmol) in ethanol (15 ml) was refluxed with thiosemicarbazide (1.9 mmol) for 3 h. The pyrazolopyrimidinethione **2a**—**c** which separated was crystallized from methanol as bright pale yellow needles; IR (ν_{max}, cm^{-1}) 1013±13 (C=S), 3135±25 (NH). MS *m/z* (relative abundance) **2a**: M^+ 303 (100), 302 (99), 187 (10), 141 (14); **2b**: M^+ 317 (89), 316 (70), 201 (30), 141 (16), 77 (100).

5-Aryl-7-mthylthio-2-phenylpyrazolo[1,5-*c*]pyrimidines (3) (Tables 1—3). A solution of **2a**—**c** (0.6 mmol) in dry acetone (10 ml) was refluxed with methyl iodide (1.61 mmol) and anhydrous potassium carbonate (2 g) for 6 h. The reaction mixture was then poured into cold water and the separated product **3a**—**c** was filtered, dried, and crystallized from methanol as needles; IR (ν_{max}, cm^{-1}) 1575—1620 (C=N), 1512—1535 (pyrimidine C=C).

2,5-Diphenyl-3-halopyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones 4 and 5 (Tables 1—3). A solution of bromine (1.6 mmol) or iodine monochloride (1.4 mmol) in chloroform (10 ml) was gradually added to a suspension of **2a** (1.3 mmol) in chloroform (10 ml) with stirring for 30 min at room temperature. The precipitated 3-halo thione **4** or **5** was filtered, washed with methanol, dried, and crystallized from benzene or chloroform–methanol as pale yellow needles; IR (ν_{max}, cm^{-1}) 1025—1031 (C=S), 1583—1620 (C=N), 1497—1523 (pyrimidine C=C), 3430—3500 (NH).

5-Aryl-3-nitro-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (6) (Tables 1—3). A mixture of nitric (*d* 1.41; 1 ml) and sulfuric (*d* 1.84; 1 ml) acids in glacial acetic acid (10 ml) was gradually added to a solution of **2a—c** (1.2 mmol) in glacial acetic acid (10 ml) with stirring for 3 h at room temperature. The reaction mixture was then poured into cold water with stirring and the precipitated 3-nitro derivative **6a—c** was filtered, washed with water, and dried. The crude product was purified by boiling with ethanol to give yellow needles; IR (ν_{max}, cm^{-1}) 1018—1028 (C=S), 1347—1352 and 1502—1525 (NO_2), 1538—1610 (C=N), 1475—1490 (pyrimidine C=C), 3400—3480 (NH). MS *m/z* (relative abundance) **6b**: M^+ 362 (10), 316 (14), 201 (15), 187 (70), 83 (100), 77 (10).

7,7′-Dithiobis[5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine]s (7) (Tables 1—3). A solution of **2a—c** (1.2 mmol) in glacial acetic acid (20 ml) was treated portionwise with a 25% aqueous solution of sodium nitrite (10 ml). The mixture was heated on a boiling water bath with stirring for 30—60 min, whereby a yellow solid started to separate. The reaction mixture was then diluted with water and the precipitated **7a—c** was filtered and crystallized from benzene as yellow needles; IR (ν_{max}, cm^{-1}) 1570—1617 (C=N), 1495—1505 (pyrimidine C=C).

7,7′-Dithiobis[5-aryl-3-phenylazo-2-phenylpyrazolo[1,5-*c*]pyrimidine]s (8) (Tables 1—3). An aqueous solution of sodium hydroxide (8 ml, 10%) was added to a suspension of **2a—c** (1.5 mmol) in ethanol (15 ml). The reaction mixture was gradually treated with a solution of benzenediazonium chloride (prepared from 1 ml of aniline) at 5 °C with stirring for 1 h. The disulfides **8a—c**, so formed, were collected by filtration and crystallized from ethanol as reddish brown needles; IR (ν_{max}, cm^{-1}) 1580—1638 (C=N), 1525—1551 (pyrimidine C=C).

5-Aryl-2-phenylpyrazolo[1,5-*c*]pyrimidin-7(6*H*)-ones (9) (Tables 1—3). A mixture of **2a—c** (1.5 mmol), 30% hydrogen peroxide (4 ml) and 10% aqueous sodium hydroxide (18 ml) was heated on a boiling water bath for 2—3 h. The pH of the resulting solution was adjusted to 6 by addition of concentrated hydrochloric acid. The precipitated ketone **9a—c** was washed several times with water, dried, and crystallized from methanol as pale yellow needles; IR (ν_{max}, cm^{-1}) 1582—1645 (C=N), 1502—1525 (pyrimidine C=C), 1690—1720 (C=O), 3380—3420 (OH).

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