Preparation and Reactions of 6-Aryl-1,5-dihydro-3-phenyl-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones

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The title compounds have been prepared in excellent yields by the reaction of 5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones with potassium hydroxide. The reactions of these pyrazolopyridones have been investigated. The ring system readily undergoes electrophilic substitution at the 7-position. They are converted to the corresponding pyrazolopyridinethiones on reaction with phosphorus pentasulfide. The structures of the above compounds were elucidated by their spectral characteristics.

Pyrazolo[4,3-*c*]pyridines have continued to attract interest owing to their structural relationship to antagonistic purine bases[1] and guanines[2] as well as biological interest. Thus, some of these compounds show fungicidal and antibacterial,[3] antiinflammatory,[4] tranquilizing, and antiasthmatic activities.[5] However, the synthesis of this ring system has been achieved in only a limited number of ways,[6] mostly involving the use of either 4-hydrazinopyridines or pyrazoles containing carboxylic acid functions at positions 3 and 4 as starting materials. Recently, some derivatives of the pyrazolo[4,3-*c*]pyridine ring system have been prepared by reaction of an iminophosphorane with suitable reagents.[7] The generality of most of these methods are impaired by the availability of the starting materials. In the present study, a new method for the synthesis of 6-aryl-1,5-dihydro-3-phenyl-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones (**2**) from 5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (**1**) has been developed. The latter compounds, which are also useful as starting materials for the synthesis of some derivatives of the pyrazolo[1,5-*c*]pyrimidine ring system,[8] were prepared by reaction of 1,5-diaryl-4-pentyne-1,3-diones with thiosemicarbazide.[8]

Treatment of 5-aryl-2-phenylpyrazolo[1,5-*c*]pyrimidine-7(6*H*)-thiones (**1a—e**) with potassium hydroxide in boiling ethanol gave the corresponding 6-aryl-1,5-dihydro-3-phenyl-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones (**2a—e**) in excellent yields. The IR spectra of the pyrazolopyridones **2** exhibited, besides a strong carbonyl-stretching band in the region 1713—1740 cm^{-1}, a strong C=N absorption in the range 1621—1632 cm^{-1} as well as C=C and NH absorptions (cf. Experimental). The absence of OH absorption in their spectra indicates that in the solid state the lactam form predominates over the lactim one.

The ^1H NMR spectra of **2** (Table 1) showed a singlet at δ=7.33—7.50 for the H-7 ring proton, in almost the same region reported for several pyrazolo[4,3-*c*]pyridines,[9] and an exchangeable singlet at δ=13.00—13.30 for the pyrazole NH proton. Moreover, besides the pyridine ring NH proton at δ=11.15—11.53, a broad singlet singal (δ=8.46—8.55) which may suggest some contribution of the enol form was observed. The assignment of the NH signals to this bicyclic system is supported by the reported data for 1,5-dihydro-4*H*-pyrazolo[4,3-*c*]-pyridin-4-ones.[9] Further support of the structure of the pyrazolopyridones was obtained from their mass spectra. The compound **2b** gave a relatively intense molecular ion peak together with a series of peaks characteristic of pyrazolopyridones (cf. Experimental).

Halogenation, nitrosation, and sulfonation of the pyrazolo[4,3-*c*]pyridine ring system have not been reported previously. With the aim of repairing this gap. I studied, in the first instance, the behavior of 3,6-diaryl-1,5-dihydro-4*H*-pyrazolo[4,3-*c*]-pyridin-4-ones towards some representative electrophilic reagents. Bromination of **2a—c,e** with bromine and iodination of **2a—e** with iodine monochloride gave the respective 7-bromo **3a—c,e** and 7-iodo **4a—e** derivatives. Moreover, nitrosation of **2b,e** with sodium nitrite in hot glacial acetic acid, and sulfonation with fuming sulfuric acid led to the formation of the corresponding 7-nitroso **5b,e** and 7-sulfonic acid derivatives **6b,e**. The pyrazolopyridones **2** also underwent other electrophilic substitution at the 7-position. The 7-nitro **7a—e** and 7-phenylazo compounds **8b,e** were obtained in excellent yields on treatment of **2a—e** with nitric and sulfuric acids in hot glacial acetic acid, and **2b,e** with benzenediazonium chloride in the presence of sodium hydroxide, respectively (Scheme 1). The structures of all above 7-substituted compounds were confirmed from their spectral and analytical data (Table 1). These pyrazolopyridones **2** are therefore useful starting materials for the preparation of pyrazolo-[4,3-*c*]pyridines carrying a nuclear nitro or phenylazo group of which only a few examples are reported in the literature.[1,10] The formation of the pyrazolopyridones **2** is assumed to proceed by pyrimidine ring opening in **1** by hydroxide ion and subsequent ring-closure with rearrangement (Scheme 1). It is worth mentioning here that a similar mechanism was suggested for the formation of pyrazolo[3,4-*b*]pyridines by the reaction of pyrazolo[1,5-*a*]pyrimidin-7-ones with sodium hydroxide.[11] Evidently, the above reaction provides a convenient and apparently general method for the preparation of pyrazolo[4,3-*c*]pyridones carrying aryl substituents of which only a few examples are reported in the literature.[6]

The pyrazolo[4,3-*c*]pyridones **2**, bearing a carbonyl group appeared attractive intermediates for the synthe-

Table 1. Analytical and ^{1}H NMR Spectral Data of Pyrazolopyridine Derivatives

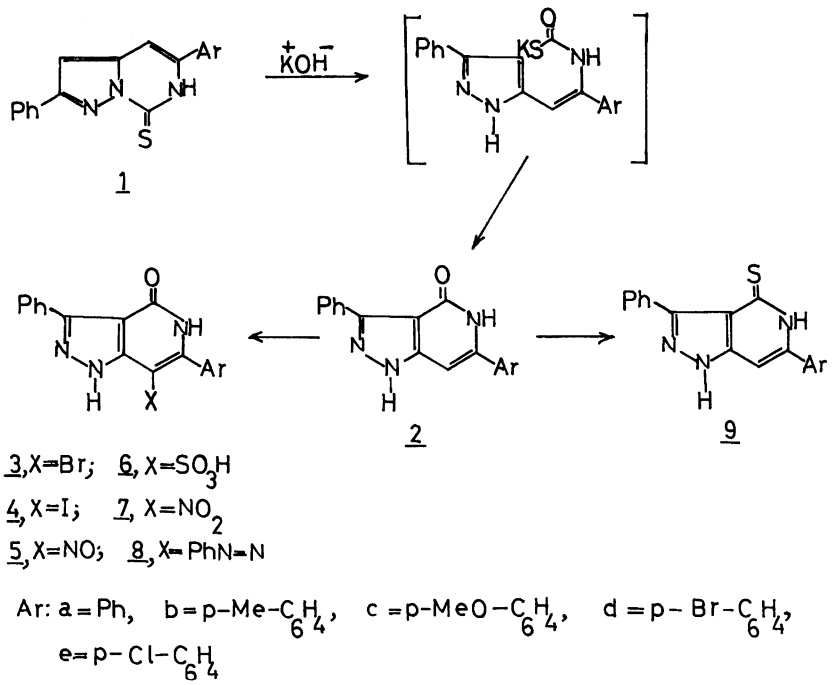
Compd No.	Mp °C	Yield %	Molecular formula	Analysis Calcd/Found (%) C	H	N	S	X	Solvent	Chemical Shifts (δ/ppm)[a] H-7 (s)	$NH_{1,5}$[b] (s, 2H)	ArH (m)	Others (s)
2a	248—250	90	$C_{18}H_{13}N_3O$	75.3	4.5	14.6			DMSO-d_6	7.50	11.53, 13.11	7.63	8.55 (OH)[b]
				(75.6	4.3	14.8		)					
2b	378—380	84	$C_{19}H_{15}N_3O$	75.8	5.0	14.0			DMSO-d_6	7.40	11.48, 13.00	7.40	2.33 (3H, CH_3)
				(75.5	4.8	13.7		)					8.46 (OH)[b]
2c	220—221	88	$C_{19}H_{15}N_3O_2$	71.9	4.7	13.3			DMSO-d_6	7.45	11.15, 13.13	7.31	3.92 (3H, OCH_3)
				(71.7	4.9	13.6		)					8.52 (OH)[b]
2d	265—268	93	$C_{18}H_{12}BrN_3O$	59.0	3.3	11.5		21.9	DMSO-d_6	7.33	11.18, 13.30	7.46	
				(59.3	3.5	11.8		21.5)					
2e	243—245	95	$C_{18}H_{12}ClN_3O$	67.2	3.7	13.1		11.0	DMSO-d_6	7.35	11.19, 13.20	7.52	
				(67.4	3.9	12.8		11.4)					
3a	122—125	85	$C_{18}H_{12}BrN_3O$	59.0	3.3	11.5		21.9	C_5D_5N			7.80	
				(59.4	3.1	11.2		21.2)					
3b	225—227	90	$C_{19}H_{14}BrN_3O$	60.0	3.3	11.1		21.1	C_5D_5N			7.76	2.35 (3H, CH_3)
				(60.3	3.4	11.3		21.5)					
3c	245—248	95	$C_{19}H_{14}BrN_3O_2$	57.6	3.5	10.6		20.2	C_5D_5N			7.60	3.90 (3H, OCH_3)
				(57.3	3.3	10.8		20.7)					
3e	326—327	87	$C_{18}H_{11}BrClN_3O$	53.9	2.8	10.5		20.0, 8.4	C_5D_5N			7.82	
				(54.3	2.7	10.7		19.6, 9.1)					
4a	225—227	83	$C_{18}H_{12}IN_3O$	52.3	2.9	10.2		30.8	C_5D_5N			7.65	
				(52.6	3.0	9.8		30.6)					
4b	230—231	95	$C_{19}H_{14}IN_3O$	53.4	3.3	9.8		29.7	C_5D_5N			7.78	2.36 (3H, CH_3)
				(53.7	3.3	9.5		30.2)					
4c	215—217	88	$C_{19}H_{14}IN_3O_2$	51.5	3.2	9.5		28.7	C_5D_5N			7.55	3.93 (3H, OCH_3)
				(51.3	3.2	9.8		29.1)					
4d	221—222	75	$C_{18}H_{11}BrIN_3O$	44.0	2.2	8.5		16.3, 25.8	C_5D_5N			7.62	
				(44.3	2.2	8.3		16.0, 26.1)					
4e	207—210	79	$C_{18}H_{11}ClIN_3O$	48.3	2.5	9.4		8.0, 28.4	C_5D_5N			7.67	
				(48.0	2.6	9.2		8.5, 28.0)					
5b	250—252	66	$C_{19}H_{14}N_4O_2$	68.0	4.4	17.6			C_5D_5N			7.88	2.37 (3H, CH_3)
				(68.3	4.4	17.3		)					
5e	243—244	70	$C_{18}H_{11}ClN_4O_2$	61.6	3.1	16.0		10.1	C_5D_5N			7.52	
				(61.9	3.0	16.3		9.6)					
6b	162—163	65	$C_{19}H_{15}N_3O_4S$	59.8	3.9	11.0	16.8		DMSO-d_6			7.49	2.32 (3H, CH_3)
				(60.2	3.8	11.3	16.5	)					
6e	152—155	67	$C_{18}H_{12}ClN_3O_4S$	53.8	3.0	10.5	16.0	8.8	DMSO-d_6			7.70	
				(54.0	3.1	10.7	15.6	8.5)					
7a	>300	87	$C_{18}H_{12}N_4O_3$	65.1	3.6	16.9			DMSO-d_6			7.77	
				(64.9	3.3	17.1		)					
7b	295—297	89	$C_{19}H_{14}N_4O_3$	65.9	4.1	16.2			DMSO-d_6			7.55	2.36 (3H, CH_3)
				(65.7	4.0	16.4		)					
7c	188—190	83	$C_{19}H_{14}N_4O_4$	63.0	3.9	15.5			DMSO-d_6			7.81	3.76 (3H, OCH_3)
				(63.3	4.0	15.1		)					
7d	>300	79	$C_{18}H_{11}BrN_4O_3$	52.6	2.7	13.6		19.5	DMSO-d_6			7.64	
				(52.9	2.6	13.4		19.0)					
7e	>300	86	$C_{18}H_{11}ClN_4O_3$	59.0	3.0	15.3		9.7	DMSO-d_6			7.19	
				(58.7	3.1	15.5		10.1)					
8b	120—122	90	$C_{25}H_{19}N_5O$	74.1	4.7	17.3			$CDCl_3$			7.66	2.23 (3H, CH_3)
				(74.4	4.8	17.0							
8e	92—95	85	$C_{24}H_{16}ClN_5O$	65.2	3.6	15.9		8.0	$CDCl_3$			7.42	
				(65.5	3.7	16.1		7.6)					
9d	288—290	78	$C_{19}H_{15}N_3S$	70.6	4.6	14.9	10.0		DMSO-d_6	7.53	10.60, 13.52	7.60	2.28 (3H, CH_3),
				(70.3	4.7	14.6	10.3	)					4.14 (SH)[b]
9e	271—273	75	$C_{18}H_{12}ClN_3S$	62.9	3.3	14.0	9.5	10.3	DMSO-d_6	7.62	10.12, 13.60	7.83	
				(63.2	3.3	14.3	9.8	10.0)					

a) s: Singlet, m: Multiplet. b) Exchangeable with D_2O.

sis of pyrazolo[4,3-*c*]pyridines having reactive functional groups in 4 position. In the present study, the reactions of **2b** and **2e** with phosphorus pentasulfide was examined. When **2b** or **2e** was refluxed with phosphorus pentasulfide in dry benzene, the starting material was recovered. However, the respective 1,5-dihydro-4*H*-pyrazolo[4,3-*c*]pyridine-4-thiones **9b** and **9e** were obtained in high yield when **2b** and **2e** were treated with phosphorus pentasulfide in boiling dry pyridine. The structure of **9** was confirmed from their spectral and analytical data (Table 1).

Experimental

General Methods. Melting points were determined with a kofler block and are uncorrected. Elemental microanalyses were performed in the Microanalysis Unit, Cairo University, Cairo. The infrared (IR) spectra were measured



Scheme 1.

with a Unicam SP 1025 spectrophotometer for potassium bromide pellets. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 NMR spectrometer at 90 MHz with TMS as internal standard. Mass spectra (MS) were recorded at 70 eV with an AEI MS-9 spectrometer coupled to a DS-50 Data system using a direct insertion probe for introduction of samples. Thin layer chromatography (TLC) were done on Merck Kieselgel 60-F 254 precoated plastic plates.

6-Aryl-1,5-dihydro-3-phenyl-4*H*-pyrazolo[4,3-*c*]-pyridin-4-ones (2) (Table 1). A suspension of **1a**—**e**[8] (0.6 mmol) in ethanol (10 ml) was heated under reflux with 10% aqueous potassium hydroxide solution (4 ml) for 30—33 h. The reaction mixture was diluted with water, and acidified with concentrated hydrochloric acid (5 ml). The precipitated ketone **2a**—**e** was collected, washed several times with water, dried, and crystallized from ethanol as needles: IR (ν_{max}, cm^{-1}) 3091—3176 and 3180—3191 (two NH), 1536—1609 (C=C). MS *m/z* (relative abundance) **2b**: 301 (M^+), 300 (M^+−H), 258 (M^+−HCNO), 197 (M^+−PhCN−H), 142 (M^+−HCNO−HC≡C−C_6H_4−Me-*p*), 116 (HC≡C−C_6H_4−Me-*p*), 103 (PhCN), 91 (C_6H_4−Me-*p*), 77 (Ph).

6-Aryl-7-halo-1,5-dihydro-3-phenyl-4*H*-pyrazolo[3,4-*c*]pyridin-4-ones (3 and 4) (Table 1). A solution of bromine (1.2 mmol) or iodine monochloride (1.2 mmol) in chloroform (8 ml) was gradually added to a suspension of **2** (1.1 mmol) in chloroform (8 ml) with stirring for 20 min at room temperature. The precipitated 3-halo ketone **3a**—**c**,**e** or **4a**—**e** was collected by filtration, washed with methanol, dried, and crystallized from benzene as needles; IR (ν_{max}, cm^{-1}) 3095—3183 and 3192—3200 (two NH), 1725—1762 (C=O), 1625—1540 (C=N), 1540—1615 (C=C).

6-Aryl-1,5-dihydro-7-nitroso-3-phenyl-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones (5) (Table 1). A suspension of **2b**,**e** (0.8 mmol) in glacial acetic acid (12 ml) was treated portionwise with a 30% aqueous solution of sodium nitrite (6 ml). The mixture was heated on a boiling water bath with stirring for 30—45 min whereby yellow solids started to separate. The reaction mixture was then diluted with water, and the precipitated **5b**,**e** was collected by filtration and crystallized from pyridine as pale yellow needles: IR (ν_{max}, cm^{-1}); 3300—3335 and 3412—3469 (two NH), 1719—1755 (C=O), 1630—1652 (C=N), 1513—1587 (C=C).

6-Aryl-1,5-dihydro-4-oxo-3-phenyl-4*H*-pyrazolo[4,3-*c*]pyridine-7-sulfonic Acids (6) (Table 1). A solution of **2b**,**e** (1.2 mmol) in concentrated sulfuric acid (3 ml) was added dropwise at room temperature during 30 min to a stirred mixture of 20% oleum (0.16 ml) and concentrated sulfuric acid (2 ml). The mixture was heated on a boiling water bath with stirring for 30—60 min. The acidic solution was poured onto crushed ice (3 g) with swirling; the brown precipitates were collected by filtration, washed with a little cold water, and dried (P_2O_5). The solid was purified by dissolving it in saturated aqueous sodium carbonate (2 ml), extracting the solution with chloroform (2×2 ml), and acidifying the aqueous layer with concentrated hydrochloric acid (2 ml). The sulfonic acid **6b**,**e** was filtered off, washed with water, dried, and crystallized from ethanol as needles; IR (ν_{max}, cm^{-1}) 3030—3060 and 3201—3270 (two NH), 1690—1725 (C=O), 1615—1620 (C=N) 1515—1130 (C=C), 1156—1150, and 1015—1080 (SO_3H).

6-Aryl-1,5-dihydro-7-nitro-3-phenyl-4*H*-pyrazolo-[4,3-*c*]pyridin-4-ones (7) (Table 1). A mixture of nitric (d 1.41; 1 ml) and sulfuric (1.84; 1 ml) acids in glacial acetic acid (5 ml) was gradually added to a solution of **2a**—**e** (0.8 mmol) in glacial acetic acid (6 ml). The mixture was heated on a boiling water bath with stirring for 20—30 min. The reaction mixture was then poured into cold water with stirring, and the precipitated 7-nitro derivative **7a**—**e** was collected by filtration, washed with water, dried, and crystallized from pyridine-methanol as yellow needles; IR (ν_{max}, cm^{-1}) 3340—3362 and 3400—3430 (two NH), 1717—1725

(C=O), 1596—1616 (C=N), 1575—1590 (C=C), 1350—1357 and 1510—1535 (NO_2).

6-Aryl-1,5-dihydro-3-phenyl-7-phenylazo-4*H*-pyrazolo[4,3-*c*]pyridin-4-ones (8) (Table 1). An aqueous solution of sodium hydroxide (10 ml, 10%) was added to a suspension of **2b,e** (1.3 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 2 h. The 7-phenylazo derivative **8b,e** so formed, was collected by filtration and crystallized from methanol as reddish brown needles: IR (ν_{max}, cm^{-1}) 3119—3130 and 3200—3222 (two NH), 1692—1710 (C=O), 1612—1615 (C=N), 1570—1585 (C=C).

6-Aryl-1,5-dihydro-3-phenyl-4*H*-pyrazolo[4,3-*c*]-pyridine-4-thiones (9) (Table 1). A solution of **2b,e** (0.4 mmol) in dry pyridine (20 ml) was refluxed with phosphorus pentasulfide (0.9 mmol) for 3 h. The reaction mixture was worked up as described earlier.[9] The isolated thiones **9b,e** was crystallized from benzene–petroleum ether (bp 60—80°C) as pale yellow prisms: IR (ν_{max}, cm^{-1}) 3210—3223 and 3232—3300 (two NH), 1611—1628 (C=N), 1556—1629 (C=C), 1110—1150 (C=S).

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