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SYNTHESIS AND SOME REACTIONS OF 4-AROYL-6-ARYL PYRIDAZIN-3(2H)-THIONES

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SYNTHESIS AND SOME REACTIONS OF 4-AROYL-6-ARYL PYRIDAZIN-3(2H)-THIONES

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4-Aroyl-3-chloro-6-arylpyridazines^[1] (**1**) react with thiourea to give 4aroyl-6-arylpyridazin-3 (**2H**)-thiones (**2**) respectively^[2-7]. The compounds **2** reacted with dimethyl sulphate, hydrazine hydrate and hydroxylamine hydrochloride to give 4-aryol-6-aryl-3-methylthiopyridazines **5**, pyrazolinopyridazines **7** and isoxazolopyridazine **8**, respectively. The compounds **2a-c** reacted in alkaline ammonium hydroxide solution with sodium hypochlorite solution to give the isothiazolopyridazines **10a-c**.

Keywords: 4-aryol-3-chloro-6-arylpyridazines; dimethyl sulphate; hydrazine hydrate; hydroxylamine hydrochloride; sodium hypochlorite

INTRODUCTION

A series of publications^[2-17] dealing with the synthesis and the reactivity of pyridazin-3(**2H**)-thiones involving positions 2 and 3 upon treatment with different alkylating and acylating reagents has been found in the literature. Our interest is now directed to investigate the reactivity of 4aroylpyridazin-3(**2H**)-thione derivatives (**2a-c**) towards some nucleophilic reagents utilizing the presence of thiocarbonyl and aroyl carbonyl groups at adjacent carbon atoms.

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RESULTS AND DISCUSSION

4-Aroyl-3-chloro-6-arylpyridazines (1) (their synthesis was reported recently^[1]) react with thiourea^[2-7] in boiling ethanol to give 4-aryol-6-arylpyridazin-3(2H)-thiones (2) in good yields. The reactions proceeded, presumably, via the intermediate formation of thiuronium salts (3) which have not been isolated.

This suggests that the reactions instead of involving the aroyl carbonyl group at position 4 occur at position 3.

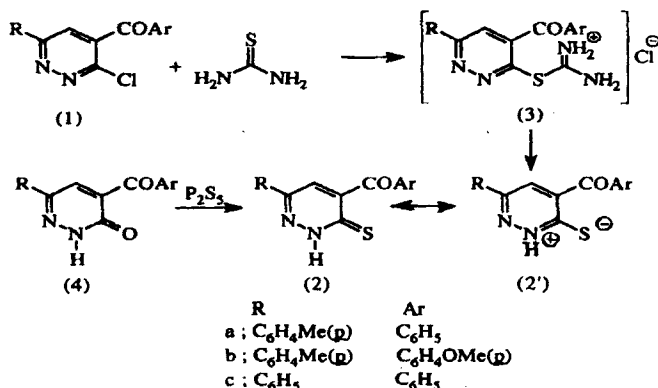


TABLE I

Compd.	M.P. °C	Yield (%)	M.F	Analysis %		Found/Calcd.	
				C	H	N	S
2a	264–266	87	C ₁₈ H ₁₄ N ₂ OS	70.30	4.70	9.30	10.20
				70.58	4.57	9.15	10.45
2b	268–270	91	C ₁₉ H ₁₆ N ₂ O ₂ S	67.60	5.00	8.10	9.20
				67.85	4.76	8.30	9.52
5a	149–150	55	C ₁₉ H ₁₆ N ₂ OS	71.00	4.90	8.80	
				71.31	5.00	8.75	
5b	153–155	60	C ₂₀ H ₁₈ N ₂ O ₂ S	69.00	5.00	8.00	
				68.57	5.14	8.00	
5c	130–132	52	C ₁₈ H ₁₄ N ₂ OS	70.90	4.40	8.90	
				70.58	4.57	9.15	
7a	220–222	52	C ₁₈ H ₁₄ N ₄	75.20	4.90	19.45	
				75.52	4.89	19.58	
7b	268–269	55	C ₁₉ H ₁₆ N ₄ O	72.00	5.10	18.19	
				72.15	5.06	17.72	

Compd.	M.P. °C	Yield (%)	M.F	Analysis %		Found/Calcd.	
				C	H	N	S
8a	160–162	50	C ₁₈ H ₁₃ N ₃ O	75.60	4.30	14.20	
				75.26	4.52	14.63	
8b	197–199	52	C ₁₉ H ₁₅ N ₃ O ₂	71.60	4.50	13.40	
				71.92	4.73	13.24	
10a	126–127	57	C ₁₈ H ₁₃ N ₃ S	71.10	4.20	13.45	10.40
				71.28	4.29	13.86	10.56
10b	164–165	65	C ₁₉ H ₁₅ N ₃ OS	68.79	4.39	12.30	9.40
				68.46	4.50	12.61	9.60
10c	140–142	50	C ₁₇ H ₁₁ N ₃ S	70.36	3.50	14.71	10.90
				70.58	3.80	14.53	11.70

The structure of thiones (**2**) was additional to the analytical data, derived from the fact that they dissolve readily in aqueous sodium hydroxide solution and reprecipitate upon addition of mineral acids. Their infrared spectra show strong carbonyl absorption of aryl ketones at 1672 cm⁻¹ and 1665 cm⁻¹ (Table II) and broad bands at 3070.2840 cm⁻¹ characteristic of the grouping (Table II).

Similar results for infrared spectra of 4-aryl-6-phenylpyridazin-3(2H)thiones and pyridazin-3(2H)-thiones were recently reported^[3,7]. ¹HNMR spectra of **2a-c** provides a good support for the proposed structure (c.f, Table II). The structure was further confirmed by the fact that **2b** was found to be identical with the product formed by the action of phosphorus pentasulphide^[8–11] on 4-(p-methoxybenzoyl)-6-p-tolylpyridazin-3(2H)-one (**4b**).



Moreover these compounds undergo many reactions characteristic of pyridazin-3(2H)-thiones. Thus 4-aryl-6-arylpyridazin-3(2H)-thiones (**2a-c**) were readily methylated on treatment with dimethyl sulphate in alkaline medium. The reaction involved the mercaptopyridazine form (**2'**) yielding 4-aryl-6-aryl-3-methylthiopyridazines (**5a-c**) and no products of the type (**6**).

The structure of (**5a-c**) was established from microanalytical data and their infrared spectra which lack the significant absorptions of NH, OH and C=S groups, while they show strong absorption of aryl ketonic

groups (c.f. Table II). Furthermore ^1H NMR spectra of -SMe group exhibit two singlets at δ 2.77 ppm and 2.60 ppm for **5b** and **5c** respectively (c.f. Table II).

TABLE II

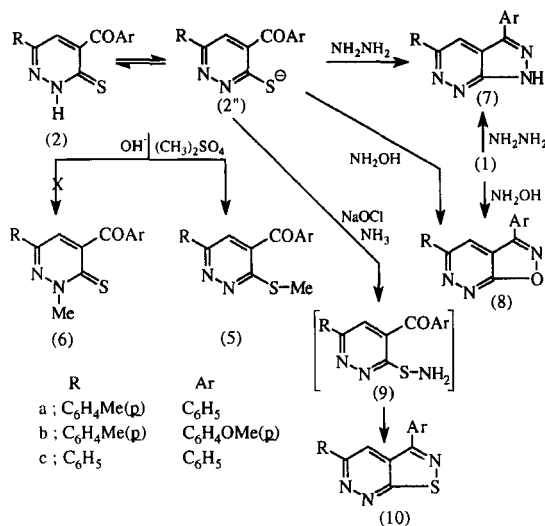
Compd.	Characteristic signals in V cm^{-1} (assignment)		^1H NMR Spectral data δ -ppm (assignment)
2a	3045–2860 (CSNH)	1672 (CO)	15.27 (s,1H,NH), 8.28–7.41 (m, Ar H's), 2.46 (s,3H, Me).
2b	3050–2840 (CSNH)	1665 (CO)	15.27 (s,1H,NH), 8.22–7.13(m, Ar H's), 3.95 (s,3H, OMe), 2.46 (s,3H, Me),
2c	3060–2855 (CSNH)	1660 (CO)	15.33 (s,1H,NH), 8.31–7.61(m, Ar H's).
5a		1665 (CO)	
5b		1665 (CO)	8.26–7.18 (m, Ar H's), 3.97 (s,3H, OMe), 2.77 (s, 3H, SMe), 2.48 (s, 3H, Me).
5c		1670 (CO)	8.34–7.63 (m, Ar H's), 2.60 (s, 3H, SMe).
7a	3300–2800 (-NH)		14.59 (s,1H,NH), 8.90–7.40 (m, Ar H's) , 2.48 (s, 3H , Me).
7b	3300–2800 (-NH)		14.20 (s,1H,NH), 8.81–7.42(m , Ar H's), 3.90 (s,3H, OMe), 2.50 (s,3H, Me).
8a		1655 (CN)	8.01–7.30(m, Ar H's), 2.45(s,3H, Me).
8b		1650 (CN)	9.09–7.27 (m , Ar H's), 3.98 (s, 3H, OMe) ,2.51 (s,3H, Me)
10a		1645 (CN)	8.81–7.44 (m, Ar H's), 2.48 (s, 3H, Me).
10b		1645 (CN)	8.85–7.25 (m, Ar H's), 3.97 (s. 3H, OMe), 2.50 (s,3H,Me).

The presence of aroyl and thione groups in (**2**) at adjacent carbon atoms creates a suitable situation for the synthesis of some fused pyridazine derivatives. Hydrazine hydrate and hydroxylamine hydrochloride react readily with **2a-c** to give pyrazolinopyridazine (**7a-c**) and isoxazolinopyridazine (**8a-c**) derivatives, respectively. The reaction evidently involved nucleophilic attack at both aroyl carbonyl and thiocarbonyl group of compounds **2** with the elimination of water and hydrogen sulfide molecules.

The structures for the compounds **7** and **8** have been elucidated by their ^1H NMR spectra. The compounds **7** exhibit signals at about 14 ppm characteristic of NH proton of pyrazoline nucleus. The structures of the prod-

ucts **7a-c** and **8a-c** were rigidly established by their identity with products obtained by the action of hydrazine hydrate or hydroxylamine hydrochloride on 4-aryl-6-aryl-3-chloro-pyridazines^[1].

When alkaline solutions of **2** were allowed to react with sodium hypochlorite solution in the presence of ammonium hydroxide, the isothiazolopyridazines **10** were readily formed in good yields. The products are suggested to be formed via the intermediate formation of compounds **9**. The structure of **10** was substantiated from microanalytical data and their infrared spectra which lack the significant absorption of NH, C=S, C-SH and CO groups. The ¹HNMR spectra of compounds **10**, show signals characteristic of aromatic protons, methyl and O-methyl groups (Table II).



Experimental

All melting points are uncorrected. Elemental analyses were performed by microanalytical unit, Ain Shams University. IR spectra (KBr discs) were obtained using a PYE Unicam Sp 1200 spectrophotometer. ¹HNMR spectra were recorded in DMSO- d_6 solutions on a Bruker AC-200 spectrometer.

Synthesis of 4-aryl-6-arylpyridazin-3(2H)-thiones (**2**)

Thiourea (0.5 g) dissolved in a minor amount of water was added to a solution of 4-aryl-3-chloro-6-arylpyridazine (1 ; 1 g) in ethanol (20 ml).

The reaction mixture was heated under reflux for 10 hrs and left to cool. The yellow solid obtained were filtered off and crystallised from glacial acetic acid to give thiones' **2** as yellow crystals (Table I).

Reaction of 4-(p-methoxybenzoyl)-6-p-tolylpyridazin-3(2H)one (4b) with phosphorus pentasulphide

A mixture of 4-(p-methoxybenzoyl)-6-p-tolylpyridazin-3 (2H)-one (**4b** 0.01 mole) and phosphorus pentasulphide (0.01 mole) in pyridine (10 ml) was heated under reflux for 7 hrs., filtered while hot, cooled and poured in dilute hydrochloric acid. The solid formed was filtered off, washed with water and crystallised from acetic acid to give (**2b**) as yellow crystals m.p. 268–70°C, yield 35%. The product showed no depression when admixed with the corresponding product obtained by the action of thiourea on 3-chloro-4-(p-methoxybenzoyl) 6-p-tolylpyridazine (**1b**).

Reaction of 4-aryl-6-arylpyridazin-3 (2H)-thiones with dimethyl sulphate ; Formation of 4-aryl-6-aryl-3-methylthiopyridazines (5a-c)

Dimethyl sulphate (0.01 mole) was added to a solution of 4-aryl-6-arylpyridazin-3(2H)-thione (**2**; 0.01 mole) in 10% aqueous sodium hydroxide solution (10 ml). The reaction mixture was heated on a boiling water-bath for one hour and left to cool. The solid formed was filtered off and crystallised from light petroleum. (b.p. 80–100°C) to give 4-aryl-6-aryl-3-methylthiopyridazines (**5a-c**) as yellow crystals (Table I).

Reaction of 4-aryl-6-arylpyridazin-3(2H)thiones with hydrazine hydrate; Formation of pyrazolinopyridazines (7)

A solution 4-aryl-6-arylpyridazin-3-(2H)-thiones (**2**; 0.01 mole) in ethanol (20 ml) was treated with hydrazine hydrate (1 ml). The reaction mixture was heated under reflux for 4 hrs. and left to coll. The solid formed was filtered off and crystallised from ethanol to give pyrazolinopyridazines (**7a-c**) as yellow crystals (Table I). The products showed no depression when admixed with the corresponding products obtained by the action of hydrazine hydrate on 4-aryl-3-chloropyridazines (**1**).

Reaction of 4-aryl-6-arylpyridazin-3 (2H)-thiones with hydroxylamine hydrochloride; Formation of isoxazolopyridazine derivatives

Hydroxylamine hydrochloride (0.12 g) dissolved in the least amount of water was added to a solution of 4-aryl-6-arylpyridazin-3(2H)-thione (**2**,

0.1 mole) in pyridine (10 ml). The reaction mixture was heated under reflux for 8 hrs., cooled and poured in dilute hydrochloric acid. The solid formed was filtered off and crystallised from ethanol to give (**8a-c**) as yellow crystals (Table I). The products showed no depression when admixed with the corresponding products obtained by the action of hydroxylamine hydrochloride on 4-aryl-6-aryl-3-chloropyridazines (**1**).

Reaction of 4-aryl-6-arylpyridazin-3(2H)-thiones with sodium hypochlorite in the presence of ammonia solution

To a stirred mixture of 4-aryl-6-arylpyridazin-3(2H)-thione (2, 1g) and ammonia solution (10 ml) in aqueous 10% sodium hydroxide solution (20 ml), 5% sodium hypochlorite solution (20 ml) was added dropwise. The reaction mixture was stirred for further 3 hrs. The yellow solid formed was filtered off and crystallised from ethanol to give isothiazolopyridazine derivatives (**10a-c**) as yellow crystals (Table I).

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