Synthesis of Some 3-substituted 6-(α-styryl) pyridazine Derivatives

M.F.ISMAIL*, N.A.SHAMS, A.M.A.EL KHAMRY AND O.E. MUSTAFA
Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt

(Received 6th November, 1983)

Summary: 3-Chloro-6-(α-styryl)pyridazines (1) react with primary amines to give 3-substituted-amino-6-(α styryl) pyridazines (2a-d)while they react with alcoholic thiourea to give 3-mercapto-6-(α styrl)pyridazines (4). The latter compounds were also prepared by the action of phosphorus pentasulphide on 6-(α-styryl) pyridazin-3 (2H)-ones (6). The reaction of 4 with alkyl iodides and acrylonitrile is also discussed.

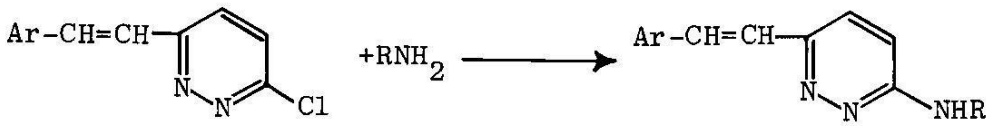
Introduction

In continuation to our previous work on pyridazines [1,2], the present investigation deals with the synthesis of some 3-substituted 6-(α -styryl) pyridazines. In an earlier publication we reported the synthesis of 3-chloro -6-(α -styryl) pyridazines (1) [3] by the action of phosphorus oxychloride on the 6-(α -styryl) pyridazin-3(2H)-ones. When 3-chloro-6-(α -styryl) pyridazines (1a & b) were allowed to react with benzylamine or aniline in the absence of solvent at elevated temperatures, good yields of 3-substituted amino-6-(α -styryl)pyridazines (2a-d) were obtained.

Results and Discussion

The structures of these products are substantiated, beside analytical data, from their infrared spectra which show the characteristic NH stretching frequencies at 3100-3290 cm^{-1} (Table 1).

The reaction of (1) with ethanolic thiourea gave high yields of 3-mercapto-6-(α-styryl)pyridazines (4a-c) or their tautomeric 6-(-styryl)pyridazin-3 (2H)-thiones [5] which were directly formed without the isolation of any thioronium salts (3), though to be intermediates in this reaction.



(1)

a, Ar=C_6H_5

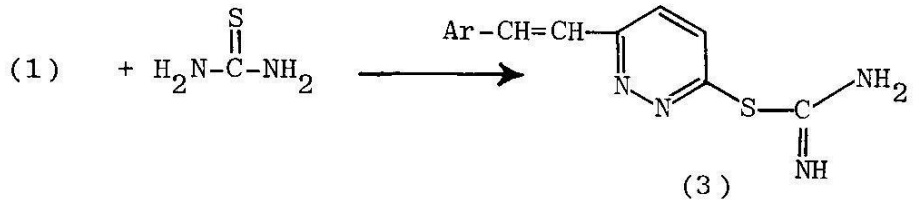
b, Ar=$C_6H_4OCH_3$(p)

(2)

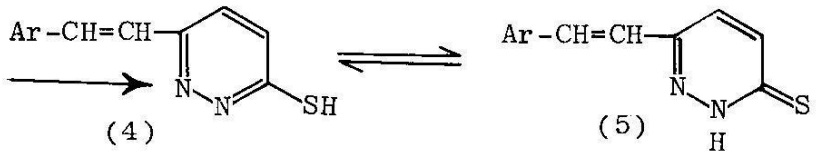
	Ar	R
a,	C_6H_5	$C_6H_5CH_2$
b,	$C_6H_4OCH_3$(p)	$C_6H_5CH_2$
c,	C_6H_5	C_6H_5
d,	$C_6H_4OCH_3$(p)	C_6H_5

Table 1

Compd	M.P. °C	Yield %	Molecular formula	Analysis % Found/Calc. C	H	N	S	IR(cm^{-1}) NH	C=N
2a	74-5	69	$C_{19}H_{17}N_3$	79.90 79.40	5.10 5.90	13.65 14.63		3220	
b	169-70	75	$C_{20}H_{19}N_3O$	75.60 75.70	5.49 5.90	13.70 13.24		3100	
c	179-80	54	$C_{18}H_{19}N_3$	79.50 79.12	5.20 5.49	14.30 15.30		3190	
d	211-12	59	$C_{19}H_{17}N_3O$	75.26 75.24	5.20 5.60	13.70 13.80		3130	
4a	236-37	75	$C_{12}H_{10}N_2S$	67.30 67.30	5.00 4.60	13.80 13.80			
b	241-42	72	$C_{13}H_{12}N_2OS$	63.10 63.39	4.90 4.91	11.25 11.47	13.40 13.11		
c	234-35	78	$C_{13}H_{12}N_2S$	68.72 68.42	4.99 5.26		13.37 14.00		
8a	131-32	75	$C_{13}H_{12}N_2S$	68.30 68.40	5.90 5.20	12.50 12.30	13.30 14.03		
b	141-42	79	$C_{14}H_{14}N_2OS$	65.94 651.0	5.00 5.40	10.59 10.80	12.80 12.40		
c	109-10	74	$C_{14}H_{14}N_2S$	- 	- 	12.20 11.57	13.00 13.22		
d	116-17	73	$C_{15}H_{16}N_2OS$	66.54 66.17	5.52 5.88	10.95 10.92	11.50 11.76		
10a	107-9	60	$C_{13}H_{12}N_2S$	68.27 68.42	5.16 5.26	12.16 12.28	13.40 14.03		
b	118-19	58	$C_{14}H_{14}N_2OS$	64.90 65.10	5.20 5.40	10.70 10.80	11.80 12.40		
11a	131-32	67	$C_{15}H_{13}N_3S$	- 	- 	15.73 15.90	- 	2260	
b	123-24	63	$C_{16}H_{15}N_3SO$	64.94 64.64	5.30 5.05	14.35 14.14	11.60 10.77	2253	

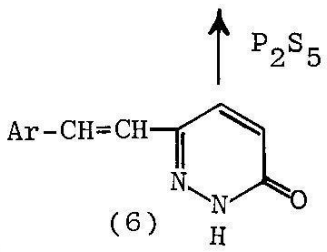


(3)

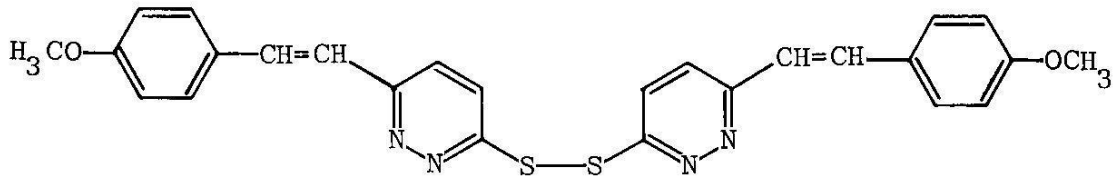


(4) (5)

a, Ar=C_6H_5
b, Ar=$C_6H_4OCH_3$(p)
c, Ar=$C_6H_4CH_3$(p)



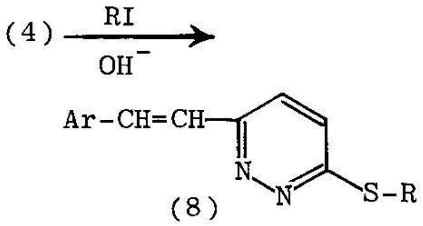
(6)



(7)

The structures of the products were inferred from: (i) micro-analytical data (ii) their solubility in aqueous sodium hydroxide solution and reprecipitation by mineral acids (iii) Their identity with the products obtained by the action of phosphorus pentasulphide on 6-(α -styryl)-pyridazin-3(2H)-ones (6).

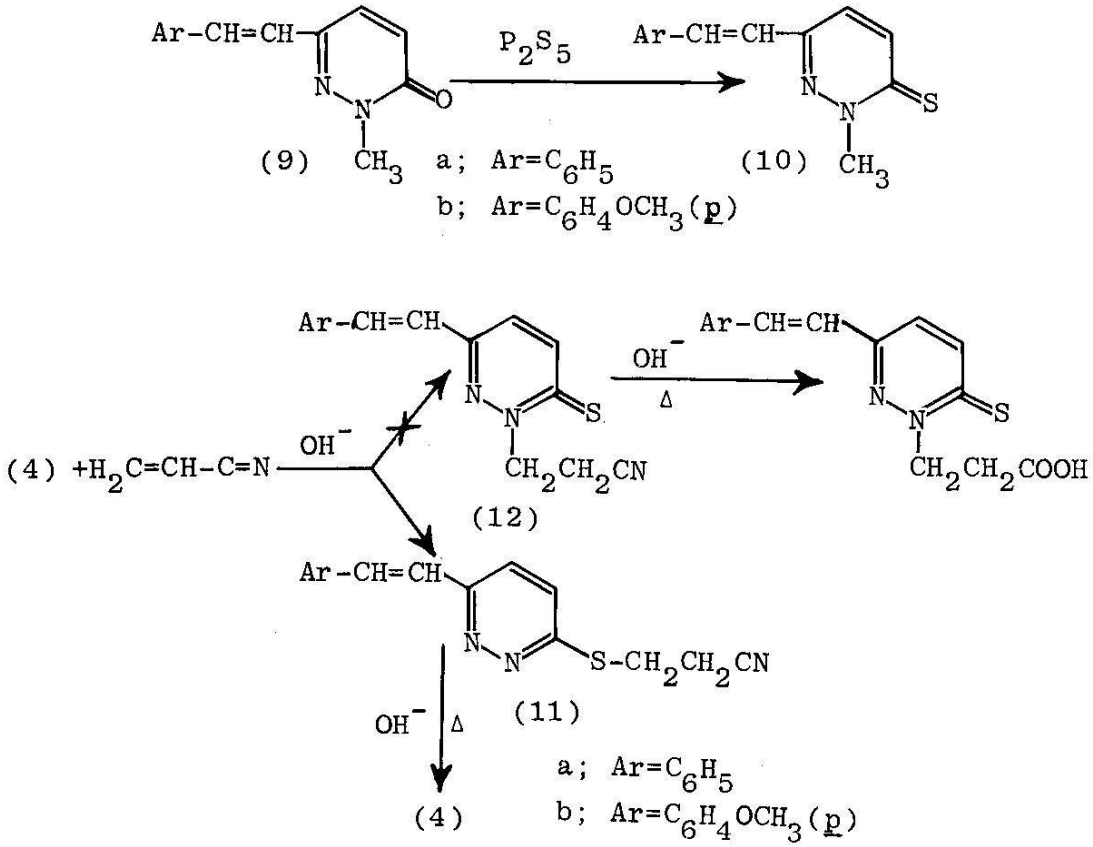
The following evidence is in favour of the 3-mercaptopyridazine structure (4) and not its tautomeric structure (5): (a) the I.R. spectra lack the NH stretching frequencies (b) Compound (4b) was easily oxidised to the disulphide (7) when treated with iodine solution. (c) The products react readily with dimethyl sulphate or methyl iodide to give 3-methylthio-6-(α-styryl)pyridazines(8a & b). They react similarly with ethyl iodide to give



(8)

R	Ar
a, CH_3	C_6H_5
b, CH_3	$C_6H_4OCH_3$(p)
c, C_2H_5	C_6H_5
d, C_2H_5	$C_6H_4OCH_3$(p)

3-ethylthio-6(-styryl)pyridazines (8c &d). The structure of (8a-d) was substantiated other than from micro-analytical data, from the fact that their I.R. spectra lack the C=S stretching frequencies. Further confirmation is



given by the fact that 8a & 8b are different from 2-methyl-6(α-styryl) pyridazine-3 (2H)-thiones 10a and 10b prepared by the action of phosphorus pentasulphide on 2-methyl-6 (α-styryl) pyridazin-3(2H)-ones 9a and 9b, respectively.

The reaction of acrylonitrile with ethanolic solution of 4a & 4b in the presence of catalytic amounts of aqueous sodium hydroxide was found to involve the 3-mercapto group to give 3-S-(2-cyanoethyl) derivatives 11a and 11b, respectively. The structure of 11 was confirmed by: (i) micro -analytical data (ii) their I.R.spectra, which show sharp bands; characteristic of C=N stretching frequencies and lack those characteristic of C=S group. (iii) Attempted hydrolysis by heating under reflux with aqueous sodium hydroxide did not lead to the formation of the expected acid but cleavage of the cyanoethyl group took place giving the parent 3-mercapto-6-(α styryl) pyridazine (4). This observation excludes the posibility of N-cyanoethyl structure (12), since compounds of this type and releated compounds undergo ready hydrolysis to the corresponding acids [4]. Similar observation were recently reported by Ismail et al. [1].

Experimental

All melting points are uncorrected. I.R. spectra were measured on a Pye Unicam 1200 and Unicam SP 200 G, using KBr disc technique. Analyses were carried out in the Research Microanalytical Laboratories of El-Nasr Company for Pharmaceutical Chemicals.

3-Substituted amino-6-(α-styryl)pyridazines (2)

Equimolar mixture of the 3-chloro 6-(α-styryl)pyridazine and the primary amine was heated in an oil bath at 160-170°C for two hours. The resulted melt was boiled with water for 15 minutes and left to cool. The colourless solid obtained was filtered off and crystallised from ethanol to give (2) as colourless crystals (Table 1).

3-Mercapto, 6-(α-styryl)pyridazines (4)

Method A: Thiourea (0.91 g., 0.021 mol) is added to a solution of 3-chloro, 6-(α-styryl)pyridazine [1] (0.01 mol.) in ethanol (30 ml.) and the mixture was heated under reflux for 5 hours. The yellow solid produced after cooling was crystalised from benzene to give (4) as yellow crystals; (Table 1).

Method B: To a solution of the 6-(α styryl)pyridazine -3(2H)-one-(0.01 mol.) in xylene (30 ml.), phosphorus pentasulphide (3.33 g., 0.015 mol.) was added and the mixture heated under reflux for 10 hours. After cooling the reaction mixture is extracted with 10% aqueous sodium hydroxide solution (20 ml.). The alkaline extracts were acidified with cold concentrated hydrochloric acid (5 ml.). The yellow solid separated was filtered off and crystallised from benzene to give (4); yield 25-30%.

Bis[6-α (p-methoxystyryl)-3-pyridazinyl] disulphide (7)

A solution of iodine in 5% potassium iodide solution was added dropwise with stirring to a solution of (4b) (2.16g, 0.01 mol.) in 10% aqueous sodium hydroxide (10 ml.) until the colour of iodine persisted. The solid formed was filtered off and crystallised from bezene to give (7) as colourless crystals, m.p. 212°, yield 30% (Found: N, 11.52; S, 13.6, $C_{26}H_{22}N_4O_2S_2$ requires: N, 11.26, S, 13.0%).

3-S-Alkyl-6-(α-styryl)pyridazines (8)

Dimethyl sulphate or alkyl iodide (015 mol.) was added dropwise to a solution of 3-mercapto-6-(α-styryl) pyridazine (4) (0.01 mol.) in 10% aqueous sodium hydroxide solution (20 ml.) and the mixture warmed for few minutes. The pale yellow solid formed was filtered off and crystallised from ethanol. (Table 1).

2-Methyl-6-(α-styryl)pyridazine-3(2H)-thiones (10)

A mixture of 2-methyl-6-(α-styryl) pyridazin-3 (2H)-one (9) (0.01 mol.) and phosphorus pentasulphide (0.015 mol.) in xylene (30 ml.) was heated for 10 hours under reflux. The reaction mixture was filtered off while hot and most of the solvent removed. The yellow solid formed was filtered off and crystallised from light petroleum (b.p. 60-80°C) (Table 1).

3-(2-Cyanoethylthio)-6-(α-styryl)pyridazine (11)

A mixture of the 3-mercapto-6-(α-styryl)pyridazine(4)(0.01 mol.) and acrylonitrile (0.64 g., 0.012 mol.) in ethanol (20 ml) is treated with few drops of 10% aqueous sodium hydroxide solution and the mixture is heated under reflux for 12 hours. The yellow solid formed after cooling was filtered off and crystallised from ethanol (Table 1).

Attempted hydrolysis of (II)

A suspension of (11) (I g.) in 20% aqueous sodium hydroxide solution (25 ml.) was refluxed till complete dissolution of the solid occurred. The clear

solution was cooled and concentrated hydrochloric acid was added till the mixture was just acidic. The yellow solid formed was filtered off and crystallised from benzene to give 3-mercapto-6-(α -styryl)pyridazine (4), identified by m.p., m.m.p. and superimposable I.R. spectra with authentic samples.

References

1. M.F.Ismail, N.A. Shams and O.M. El-Sawy, *Synthesis*, *410 (1980)*
2. M.F.Ismail, N.A.Shams, E.A.Soliman, and O.M.El-Sawy, *Ind.J.Chem.*, ***20 B***, *78 (1981)*
3. M.F.Ismail, N.A.Shams, and O.E. Mustafa, *Ind.J.Chem.*, ***21 B***, *371 (1982)*
4. V.N.Chouby, *U.A.R. J.Chem.*, ***14***, *407 (1971)*