

REACTIONS WITH CYANTHIOACETAMIDE: SYNTHESIS OF SEVERAL NEW PYRIDINE AND ANNELATED PYRIDINE DERIVATIVES

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ABSTRACT

Several new pyridine and annelated pyridine dervivatives were synthesised via the reactions of 4-aryl -6- styryl 3-cyanortetrahydropyridine -2-thiones; obtained by the action of cyanothioacetamide on some diarylidene acetone derivatives, with different reagents. structures are established on the basis of elemental analysis and spectral data studies.

Keywords:

pyridines, annelated pyridines, cyanothioacetamide.

INTRODUCTION

Cyanothioacetamide (**1**) is a versartile reagent and its chemistry has gained a considerable recent attention ¹⁻⁷. During the updating of the review ⁸ on the chemistry of **1**, I have noticed that nothing has been reported on its reaction with diarylidene acetones **2**. it was decided to investigate this reaction as a continuation to

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the effort directed towards the synthesis of heterocyclic derivatives of expected biological activities. The resulted pyridines and annelated pyridines are of value for the biological activity studies⁹⁻¹³ as well as for further chemical transformations.

RESULTS AND DISCUSSION

Thus, it has been found that equimolecular amounts of cyanothioacetamide **1** reacted with dibenzalacetone **2a** in ethanolic sodium ethoxide to afford a product of molecular formula $C_{20}H_{16}N_2S$ corresponding to the addition of **1** to one molecule of **2a** with the loss of one molecule of water. The reaction product could be formulated as the styrylpyridinethione derivative **4a** based on correct elemental analysis and spectroscopic data studies. The IR spectrum of the reaction product showed bands corresponding to the presence of NH (3200 cm^{-1}), saturated CH (2980 cm^{-1}), CN (2220 cm^{-1}), C=C (1620 cm^{-1}), and C=S (1580 cm^{-1}) groups.

The $^1\text{H-NMR}$ spectrum revealed signals corresponding to the presence of pyridine H-3 (d, 7.1 δ ppm); pyridine H-4 (d, 7.0 δ ppm) pyridine H-5 (dd, 6.4 δ ppm); two styryl CH (d, 6.2 δ ppm) in addition to the aromatic protons (m, 10H, 7.5-8.0 δ ppm) and NH (s, 1H, 8.0 ppm) in their proper positions.

In a similar manner, diethylalacetone **2b** and di-*p*-chlorobenzalacetone **2c** reacted with **1** to afford the corresponding styrylpyridinethione derivatives **4b**, respectively. The structure of

4b,c was also elucidated following the same steps as previously described in case of 4a. The formation of 4a-c in this reaction is assumed to proceed via initial addition of 1 through its active CH₂ group to the activated double bond in 2 to afford the non - isolated Michael adducts 3a-c which could then be cyclized under the applied redction conditions via enolization and loss of one molecule of water in each case to yield the final isolable 4a-c respectively.

Compounds 4a-c contain more than one active site and thus were chosen to be the starting materials for the present study through their reacions with different reagents.

Thus, each of 4a-c reacted with ethyl iodide to afford the corrd- sponding s-ethyl dervatives 5a-c respectively. Correct elemental analysis and spectral data were the basis for estblishment of the structure of 5a-c. The IR spectra of 5a-c showed the absorption bands related to the presence of CN function (2200 cm⁻¹) and the band correspoding to the presence of the C=S group was entirely absent in each case.

The ¹H-NMR spectra revealed the presence of the CH₂-CH₃ group as a triplet (1.1δppm) and a quartet (4.2 δ ppm) in each case. It is remarkable to report that the ¹H-NMR spectra of 5a-c did not reveal any signals of pyridine H-3 pyridine H-4 indicating that the reaction products suffered autoxidation under th applied reaction co- ditions.

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On the other hand, compounds 5a-c reacted with hydrazine hydrate to give a sulfur-free compound in each case. The IR spectra of these reaction products were found entirely free from the absorption band which may be attributed to the presence of the cyano function and instead the spectra showed clearly the presence of the absorption bands of an amino function in each case. Based on the above facts the reaction products could be formulated as the pyrazolo (3,4-b) pyridine derivatives 6a-c respectively. A conclusive evidence for the structure of 6a-c was achieved via their synthesis through another route. Thus, 4a-c reacted with hydrazine hydrate to afford products which were found completely identical with 6a-c in all respects (elemental analysis, m.p., mixed m.p. and spectral data) (cf. Experimental Part and Chart 1).

Compounds 4a-c reacted also with methyl chloroacetate to give products formed via the loss of hydrogen chloride which could be formulated as the methoxycarbonylmethylthio derivatives 7a-c respectively. The structure of 7a-c was proved using elemental analysis and spectral data which were found in a good agreement with the assigned structure. The ¹H-NMR spectra of 7a-c were found free from the signals corresponding to pyridine H-3 and pyridine H-4 meaning that the reaction products were autoxidised under the applied reaction conditions.

A further proof for the structure of 7a-c was achieved via their cyclization into the corresponding thieno (2,3-b) pyridine deriva-

tives δ a-c respectively, using a mixture of KOH solution and ethanol. The structure of δ a-c was, in turn, established on elemental and spectroscopic backgrounds. The IR spectra of δ a-c did not show any absorption bands related to the presence of the nitrile function or the saturated CH_2 groups which proved that both the two functions were involved in the cyclization step leading to the formation of δ a-c. On the other hand, the IR-spectra showed the presence of the band of the newly born NH_2 group at 3440, 3220 cm^{-1} in each case. The $^1\text{HNMR}$ spectra were also free from the signals characteristic for the CH_2 group.

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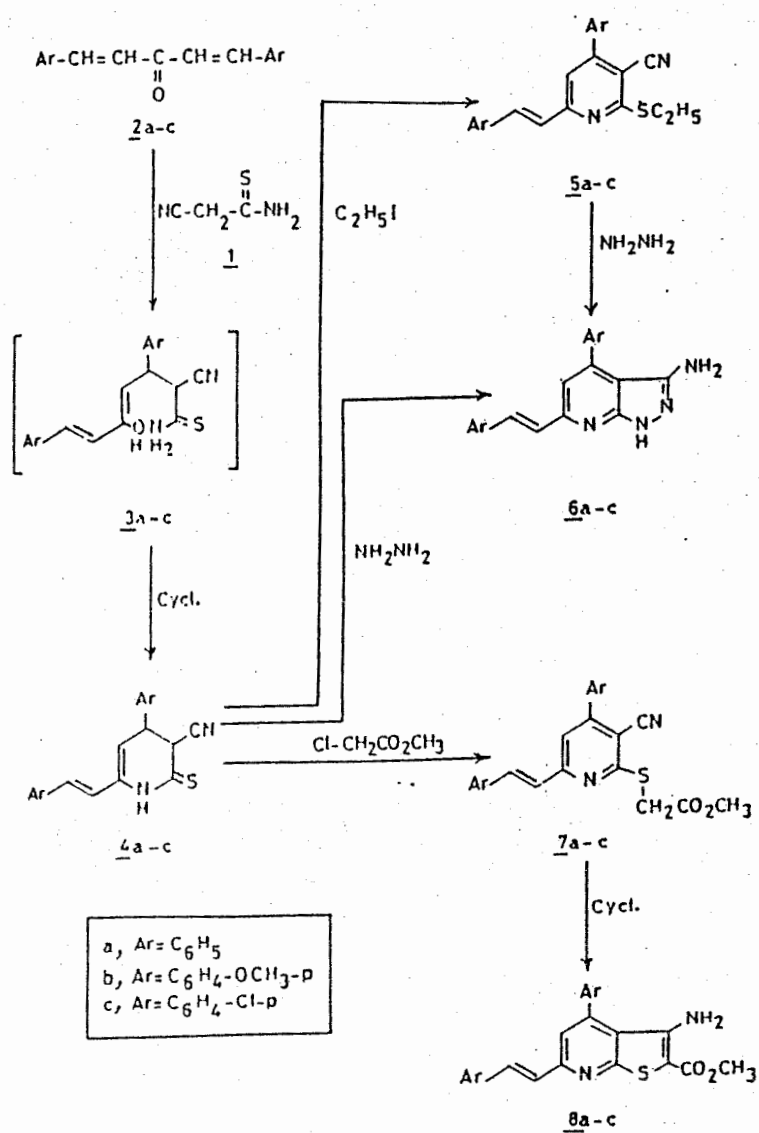


chart 1

EXPERIMENTAL

All melting points are uncorrected., IR spectra (KBr) were recorded on Pye Unicam SP.1100 spectrophotometer. $^1\text{H-NMR}$ spectra were recorded on a Varian EM 390 90 MHz spectrometer in DMSO-d_6 or CDCl_3 using TMS as an internal standard and chemical shifts are expressed as δ ppm units. Microanalyses were performed at the Microanalytical Center of Cairo University using Perkin Elmer 2400 CHN Elemental Analyzer.

Synthesis of the styrylpyridinethione derivatives 4a-c;

A solution of each of 2a-c (0.01 mole) in sodium ethoxide (prepared from 0.01 atom of sodium metal in 30 ml of absolute ethanol) was treated with 0.01 mole of 1-(cyanothioacetamide). The reaction mixture was heated under reflux for 9-10 hours. The reaction mixture was then cooled and poured into ice-cold water, then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water then crystallized from the proper solvents to afford the corresponding compounds 4a-c respectively (cf. Tables 1 and 2).

Synthesis of 5a-c

A solution of each of 4a-c (0.01 mole) in 20 % ethanolic KOH solution (20 ml) was treated with 0.01 mole of ethyl iodide. The reaction mixture was heated under reflux for 6 hours. The reaction

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mixture was cooled, poured onto ice-cold water and then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding S-ethyl derivatives 5a-c respectively (cf. Tables 1 and 2).

Synthesis of pyrazolo (3,4-b) lpyridine dervatives 6a-c

A solution of each of 4a-c or 5a-c (0.01mole) in hydrazine hydrate (15 ml.) was heated under reflux for 8 hours. The reaction mixture was cooled and poured onto ice- cold water. The sloid products obtained were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding compounds 6a-c respectively (cf. Tables 1 and 2).

Synthesis of 7a:

A solution of 4a (0.01 mole) in sodium methoxide (prepared from 0.01 atom of sodium metal in 30 ml of methanol) was treated with 0.01 mole of methyl choloacetate. The reaction mixture was heated under reflux for 6 hours, then cooled and poured onto ice-cold water. The solid product obtained after acidification with concentrated HCl was filtered off , washed with water and crystallized from ethanol to afford the methoxycarbonylmethylthio dervative 7a as a yellow product with m.p 150 °C (cf. Tables 1 and 2).

Synthesis of 7b,c:

A solution of each of 4b, c (0.01 mole) in pyridine (15 ml) was treated with 0.01 mole of methyl choloacetate. The reaction mixture was heated under rdflux for 5 hours. The reaction mixture was cooled, poued onto ice-cold water and then acidified with water concentrated HCl. The solid products obtained were filtered off, washed with and crystallized from ethanol to afford the corresponding compounds 7b,c respectively. (cf. Tables 1 and 2).

Synthesis of 8a-c:

A solution of each of 7a-c (0.01 mole) in a mixture of 20 % ethanolic KOH solution (20 ml) was heated under reflux for 5 hours. The reaction mixture was cooled, poured onto ice-cold water and then acidified with concentrated HCl. The solid products obtained were filtered off, washed with water and crystallized from the proper solvents to afford the corresponding thieno (2,3- b) pyridine derivatives 8a-c respectively (cf.Tables 1 and 2).

Table (1) : Characterisation data of the newly synthesised compounds.

Compd	Solvent and of crys- colour tallization	m.p. (°C)	yield (%)	MOL.Formula	% Analysis			Calcd. / Found		
					C	H	N	S	CI	
4a brown	Ethanol	190	68	$C_{20}H_{16}N_2S$	75.94 75.7	5.05 4.9	8.86 8.7	10.12 9.8	--	--
4b Yellow	Acetic acid	265-7	62	$C_{22}H_{20}N_2O_2S$	70.21 69.9	5.32 5.1	7.44 7.2	8.51 8.3	--	--
4c Brown	Ethanol	200-2	70	$C_{20}H_{14}N_2SCL_2$	62.34 62.1	3.63 3.5	7.27 7.4	8.31 8.5	18.44 18.3	--
5a Yellow	Ethanol	170	65	$C_{22}H_{18}N_2S$	77.19 77.3	5.26 5.4	8.18 8.0	9.53 9.5	--	--
5b Yellow	Ethanol	138	73	$C_{24}H_{22}N_2O_2S$	71.64 71.8	5.47 5.3	6.96 6.8	7.96 7.7	--	--
5c Reddish range	Acetic acid	165	78	$C_{22}H_{16}N_2SCL_2$	64.23 64.5	3.89 4.0	6.81 7.0	7.78 7.6	17.27 17.1	--

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Table (1) : Continued.

Compd and colour	Solvent of crys- tallization	m.p. (°C)	yield (%)	MOL.FOrmula	% Analysis Calcd. / Found				
					C	H	N	S	Cl
6a Yellowish brown	Ethanol	201-3	72	$C_{20}H_{16}N_4$	76.92 76.8	5.12 5.3	17.94 18.1	-- --	-- --
6b Yellow	Ethanol	235-7	68	$C_{22}H_{20}N_4O_2$	70.96 70.8	5.37 5.5	15.05 14.8	-- --	-- --
6c Yellowish brown	Ethanol	218-20	60	$C_{20}H_{14}N_4Cl_2$	62.99 62.8	3.67 3.8	14.69 14.8	-- --	18.63 18.5
7a Yellow	Ethanol	150	74	$C_{23}H_{18}N_2O_2S$	71.50 71.3	4.66 4.5	7.25 7.4	8.29 8.1	-- --

Table (1) : Continued.

Compd and colour	Solvent	m.p. of crys- tallization (°C)	yield (%)	MOL.FORMULA	% Analysis Calcd. / Found				
					C	H	N	S	Cl
7b Brown	Ethanol	162	79	C ₂₅ H ₂₂ N ₂ O ₄ S	67.26 67.4	4.93 5.1	6.27 6.1	7.17 7.3	-- --
7c Yellow	Ethanol	160	75	C ₂₃ H ₁₆ N ₂ O ₂ SCL ₂	60.65 60.4	3.51 3.4	6.15 6.3	7.3 7.2	-- --
8a Yellowish brown	Ethanol	180	63	C ₂₃ H ₁₈ N ₂ O ₂ S	71.50 71.3	4.66 4.5	7.25 7.4	8.29 8.1	15.60 15.4
8b Yellow	Ethanol	220	71	C ₂₅ H ₂₂ N ₂ O ₄ S	67.26 67.1	4.93 4.8	6.27 6.3	7.17 7.4	15.60 15.8
8C Brown	Ethanol	210	68	C ₂₃ H ₁₆ N ₂ O ₂ SCL ₂	60.65 60.4	3.51 3.4	6.15 6.3	7.03 6.9	-- --

Table 2: IR spectral data

Comp.	IR, KBr (cm ⁻¹)						
<u>4</u> a	3200 (NH);	3090 (arom. and styryl CH);	2980 (sat. CH);	2220 (CH);	1620 (C=C);	1580 (C=S)	
<u>4</u> b	3250 (NH);	3080 (arom. and styryl CH);	2980 (sat. CH);	2220 (CH);	1620 (C=C);	1580 (C=S)	
<u>4</u> c	3220 (NH);	3060 (arom. and styryl CH);	2980 (sat. CH);	2200 (CH);	1620 (C=C);	1580 (C=S)	
<u>5</u> a	3080 (arom. and styryl CH);	2980 (sat. CH);	2200 (CN);	1635 (C=N);	1600 (C=C)		
<u>5</u> b	3090 (arom. and styryl CH);	2980 (sat. CH);	2220 (CN);	1635 (C=N);	1600 (C=C)		
<u>5</u> c	3070 (arom. and styryl CH);	2980 (sat. CH);	2200 (CN);	1635 (C=N);	1600 (C=C)		
<u>6</u> a	3480, 3300, and NH ₂	3070 (arom and styryl CH);	1630 (C=N)	1610 (C=C)			
<u>6</u> b	3470, 3310, and NH ₂	3090 (arom and styryl CH);	1635 (C=N)	1610 (C=C)			
<u>6</u> c	3450, 3300, and NH ₂	3080 (arom and styryl CH);	1630 (C=N)	1610 (C=C)			
<u>7</u> a	3080 (arom. and styryl CH);	2980 (sat. CH);	2200 (CN);	1720 (ester CO);	1625 (C=N);		
<u>7</u> b	3050 (arom. and styryl CH);	2960 (sat. CH);	2210 (CN);	1720 (ester CO);	1630 (C=N);		
<u>7</u> c	3070 (arom. and styryl CH);	2970 (sat. CH);	2220 (CN);	1720 (ester CO);	1625 (C=N);		
<u>8</u> a	3440, 3220 (NH ₂);	3080 (arom and styryl CH);	1680 (ester CO);	1630 (C=N);	1610 (C=C)		
<u>8</u> b	4630, 3220 (NH ₂);	3080 (arom and styryl CH);	1762 (ester CO);	1635 (C=N);	1610 (C=C)		
<u>8</u> c	4380, 3220 (NH ₂);	3070 (arom and styryl CH);	1680 (ester CO);	1625 (C=N);	1610 (C=C)		

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