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CYANOTHIOACETAMIDE AND ITS DERIVATIVES AS SYNTHONS: SYNTHESIS OF SEVERAL NEW PYRIDINE AND PYRIDO [2, 1-b]-[1,3] THIAZINE DERIVATIVES

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Several pyridothiazine and pyridine derivatives were synthesised via the reactions 5-cyano-2, 4- dioxotetrahydropyridine-6-thione with different reagents.

Key words: Cyanothioacetamide, Pyridines, Pyrido [2,1-b] [1,3] thiazines, Diethylmalonate, Acrylonitriles.

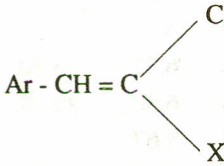
Introduction

In the last few years we have been highly interested in the chemistry of cyanothioacetamide [1] and its derivatives [1-6] and a review article dealing with the chemistry of 1 has already been published [7]. During the updating of this review, it has been observed that nothing has been reported about the reaction of 1 with diethyl malonate. It was thus decided to investigate this reaction with the objective of synthesis of several new heterocyclic derivatives required for a medicinal chemistry programme as well as for biological activity studies.

Results and Discussion

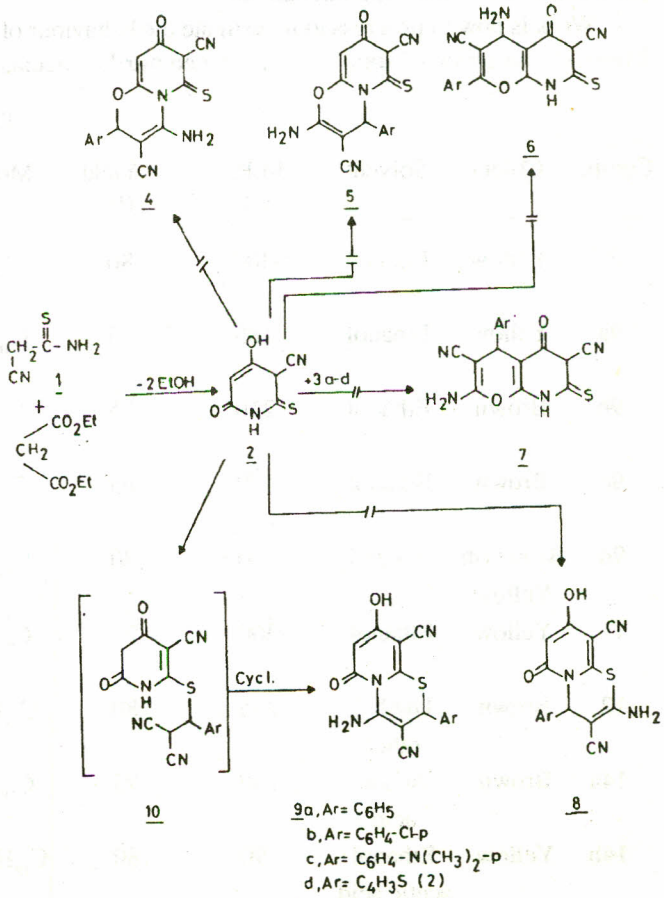
It has been found that 1 reacted, base catalysed, with diethylmalonate to afford a product of molecular formula ($C_6H_4N_2O_2S$) corresponding to the addition of one molecule of 1 to one molecule of the ester followed by the loss of two molecules of ethanol. The IR spectrum of the reaction product showed absorption bands (cm^{-1}) related to the presence of the enolic OH (3500); NH (3300); CN (2227); CO (1700) and C=S (1450). The reaction product gave also the signals (δ ppm) of OH (s, 11.9); NH (s, br, 8.6); pyridine H-3 (s, 6.0) and pyridine H-5 (s, 7.3). Based on the above data, the reaction product was formulated as the tetrahydropyridine derivative 2.

Compound 2 was taken as the starting compound for the present study due to the presence of more than one active site. Thus it has been found that 2 reacted with cinnamonitrile derivative 3a in ethanol in the presence of catalytic amount of piperidine to yield a product of molecular form $C_{16}H_{10}N_4O_2S$ corresponding to the addition of one molecule of 2 to one molecule of 3a. Several isomeric structures could, however, be assigned for the reaction product (cf. Structures 4a - 9a).



3a, Ar = C_6H_5; X = CN
b, Ar = C_6H_4-Cl-p; X = CN
c, Ar = C_6H_4-N$(CH_3)_2$-p; X = CN
d, Ar = C_4H_3S(2); X = CN
e, Ar = C_6H_5; X = CO_2Et
f, Ar = C_6H_4-Cl; X = CO_2Et

The ^{1}H-NMR spectrum of the reaction product revealed a singlet broad signal at δ12.1 ppm. Structures 4a-7a were ruled out based on the IR spectrum which showed a band at 1700 cm^{-1} (C=O) and a broad band at (2500-3200) cm^{-1} for an enolic OH group. The above findings favoured structures 9a or 8a. Depending on the Michael addition mechanism where the SH proton adds to cinnamonitrile double bond more easily than that of NH and the fact that the thiazine H-6 is highly deshielded due to the presence of neighbouring S-atom observed in ^{1}H- NMR spectra in the region of δ 7-7.8 ppm, this establishes structure 9a to represent the pdoduct of reaction of 3a with 2 and consequently ruling out structure 8a.



Scheme 1.

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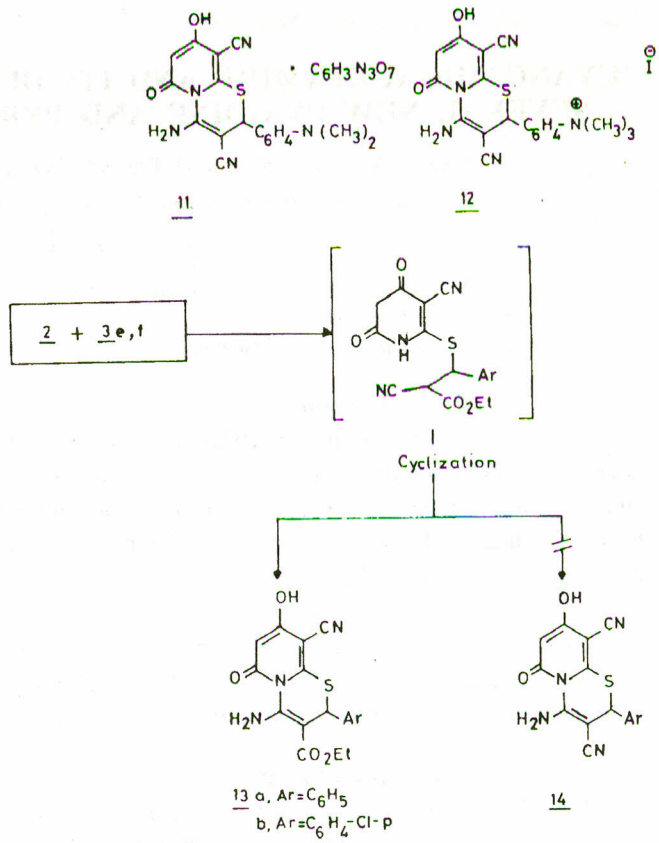
Similar to its behaviour towards 3a, compound 2 reacted with the cinnamonitriles 3b, c, d to yield also the corresponding pyrido-2,1-b 1,3 thiazine derivatives 9b, c,d respectively. The structure of 9b, c,d was also based on both elemental and spectral background. The IR and ^{1}H-NMR spectral data of 9b, c,d were in a good agreement with the assigned structure (cf. experimental part).

Moreover, compound 9c could be further characterized by the preparation of its picrate 11 and its quaternary iodide 12. The structures of both 11 and 12 were elucidated using elemental analyses and spectral data (cf. experimental part).

Moreover, compound 2 reacted with the cinnamonitrile derivatives 3e, f, under practically the same experimental conditions, to yield products corresponding to the addition of one molecule of 2 to one molecule of each of 3e, f. These reaction products could likewise be formulated as pyrido [2,1-b] [1,3]thiazine derivatives 13a, b. However, in these cases an alternative mode of cyclization through a six-membered transition structure involving the ester group (Scheme 2) is possible. Such cyclization would lead to the thiazinone derivatives 14a, b but these can be confidently excluded because the ^{1}H-NMR spectra clearly show the presence of both the ethoxyl and primary amino groups that are required by 13 (cf. Scheme 2 and the experimental part).

Work is now in progress to investigate the behaviour of 2 towards the action of some other activated nitrile reagents



Scheme 2.

TABLE 1.

Comp.	Colour	Solvent	M.P. (°C)	Yield (%)	Mol. formula	% Analysis (Calc./Found) C	H	N	S	Hal.
2.	Yellow	Ethanol	>300	80	$C_6H_4N_2O_2S$	42.85	2.38	16.66	19.05	–
						42.89	2.32	16.63	19.10	–
9a	Yellow	Ethanol	185	75	$C_{16}H_{10}N_4O_2S$	59.63	3.11	17.39	9.94	–
						59.58	3.19	17.35	9.90	–
9b	Brown	Ethanol	210	75	$C_{16}H_9N_4O_2SCl$	53.86	2.52	15.71	8.98	9.96
						53.80	2.55	15.70	8.96	9.89
9c	Brown	Ethanol	170	65	$C_{18}H_{14}N_5O_2S$	59.18	4.21	19.18	8.78	–
						59.15	4.19	19.21	8.75	–
9d	Brownish Yellow	Ethanol	>300	70	$C_{14}H_8N_4O_2S_2$	56.75	2.70	18.92	10.81	–
						56.69	2.66	18.90	10.49	–
11	Yellow	Ethanol	>300	75	$C_{24}H_{17}N_8O_9S$	48.48	3.03	18.86	5.39	–
						48.45	3.06	18.87	5.39	–
12	Brown	Diethyl ether	255	80	$C_{19}H_{17}N_5O_2SI$	45.06	3.36	18.83	6.32	25.10
						45.03	3.38	18.80	6.30	25.08
14a	Brown	Acetic acid	250	75	$C_{18}H_{15}N_3O_4S$	58.53	4.06	11.38	8.67	–
						58.50	4.10	11.35	8.69	–
14b	Yellow	Ethanol acetic acid	90	80	$C_{18}H_{14}N_3O_4SCl$	53.53	3.47	10.40	7.93	8.79
						53.51	3.48	10.42	7.95	8.77

TABLE 2.

Comp.	IR (cm^{-1})	^1H NMR (0 ppm)
2	3300 (NH); 3200-2500 (broad enolic OH); 2227 CN); 1700 (CO) and 1450 (C = S).	6.0 (s, 1H, pyridine H-3); 7.3 (3, 2H, pyridine H-5) and 8.6 (s, br, 1 H, NH).
9a	3400, 3300 (NH_2); 3200-2500 (broad enolic OH); 2220, 2227 (two CN) and 1690 (CO).	7.0-7.8 (m, 7H, ArH's, pyridine H-5 and thiazine H-6); 9.8 (s, br, 2H, 2H, NH_2) and 12.1 (s, br, 1H, OH enolic).
9b	3400, 3300 (NH_2); 3200-2500 (broad enolic OH); 2220, 2225 (two CN) and 1690 (CO).	7.0-7.7 (m, 6H, ArH's, pyridine H-5 and thiazine H-6); 9.9 (s, br, 2H, NH_2) and 12.2 (s, br, 1H, OH enolic).
9c	3400, 3300 (NH_2); 3200-2500 broad enolic OH); 2220, (CN) and 1700-1690 (two CO).	1.5 (s, 6H, two CH_3); 7.1-7.6 (m, 6H, ArH's, pyridine H-5 and thiazine H-4), 9.5 (s, br, 2H, NH_2) and 12.1 (s, br, 1H, OH enolic).
9d	3440-3300 (NH_2); 2500-3200 (broad enolic OH); 2225, 2220 (two CH) and 1710, (CO).	7.0-7.9 (m, 5H, thiophene protons, pyridine H-5 and thiazine H-4), 9.5 (s, br, 2H, NH_2), and 12.1 (s, br, 1H, OH enolic).
11	3400-3300 (NH_2); 3200-2500 (broad OH); 2227, 2220 (two CN) and 1700 (CO).	1.8 (s, 6H, three CH_3); 7.1-7.8 (m, 8H, ArH's, pyridine H-5 and thiazine H-4), 8,5 (s, br, 2H, NH_2) and 12.3 (s, br, 2H, two OH group).
12.	3450, 3310 (NH_2); 3200-2500 (broad enolic OH); 2225, 2220 (two CN) and 1700 (CO).	1.9 (s, 9H, three CH_3); 7.1-7.8 (m, 6H, ArH's, pyridine H-5 and thiazine H-4; 8.9 (s, br, 2H, NH_2 and 12.2 (s, br, 1H, OH).
14a	3410, 3320 (NH_2); 3200-2500 broad enolic OH); 2220 (CN); 1740 (CO ester) and 1700, (CO).	1.3 (t, CH_3-CH_2); 4.1 (q, 2H, CH_3 CH_2); 7.1-7.8 (m, 7H) ArH's, pyridine H-5 and thiazine H-4); 8.9 (s, br, 2H, NH_2) and 12.1 (s, br, 1H, OH enolic).
14b	3450, 3350 (NH_2); 3200-2500 (broad enolic OH); 2220 (CH); 1740 (C=O ester) and 1700 (CO).	1.3 (t, 3H, CH_3 CH_2); 4.2 (q, 2H, CH_3 CH_2); 7.0-7.8 (m, 4H. ArH's, pyridine H-5 and thiazine H-4), 8.8 (s, br, 2H, NH_2) and 12.1 (s, br, 1H, OH enolic).

and heterocycles. Some of the newly synthesised heterocyclic derivatives are now under biological screening using a number of gram negative and gram positive bacteria.

Experimental

All melting points are uncorrected. The IR spectra (KBr) were recorded on a Pye-Unicam SP-1100 spectrophotometer. ^1H-NMR spectra were recorded in DMSO-d_6 using TMS as an internal standerd on a Varian EM-390 90 MHz Spectrometer and chemical shift are expressed as δ ppm units. The microanalyses were performed at the Microanalytical Centre of Cairo University.

Synthesis of 2. A solution of cyanothioacetamide (1, 0.01 mole) in methanolic sodium methoxide solution (0.01 mole atom of sodium metal in 100 ml of methanol) was treated with diethylmalonate (0.01 mole) and the reaction mixture was heated under reflux for 4 hrs. The reaction mixture was then cooled, poured onto ice cooled water and then acidified with acetic acid. The solid obtained was thus filtered off, washed with water and then crystallized from ethanol to afford 2 (Tables 1 and 2).

Synthesis of 9a-d and 13a-b. A solution of 2 (0.01 mole) in absolute enthanol (20 ml) was treated with each of 3a-d or 3e-f (0.01 mole) in the presence of a catalytic amount of piperidine (0.5 ml) and the whole was heated under reflux for 3-4 hrs. The solid products obtained either while the reaction mixtures were still boiling or after cooling were filtered off and crystallized from a suitable solvent to yield 9a-d and 13a, b respectively (Tables 1 and 2).

Preparation of picrate 11. A solution of 9c (0.01 mole) in acetone (10 ml) was treated with a saturated solution of picric acid in the same solvent (50 ml). The reaction mixture was heated on water-bath for 2 hrs. The solid obtained on heating was filtered off and crystallized from absolute ethanol to give 11 (Tables 1 and 2).

Preparation of methiodide 12. A solution of 9c (0.01 mole) in methanol (25 ml) was treated with methyl iodide (0.015 ml) and the mixture was heated on the water-bath for 3 hrs. The reaction mixture was cooled and treated with diethyl ether whereby a solid product seperated that was collected by filteration and washed several times with diethyl ether to give 12 (Tables 1 and 2).

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