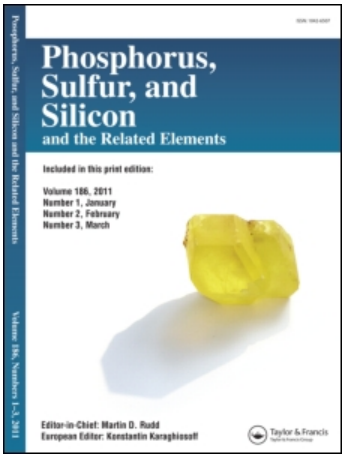

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α-CYANOTHIOACETAMIDE IN HETEROCYCLIC SYNTHESIS: A NEW APPROACH FOR THE SYNTHESIS OF 4-OXO-4,5-DIHYDRO-1,3-THIAZOLE-2-THIOACETAMIDE DERIVATIVES

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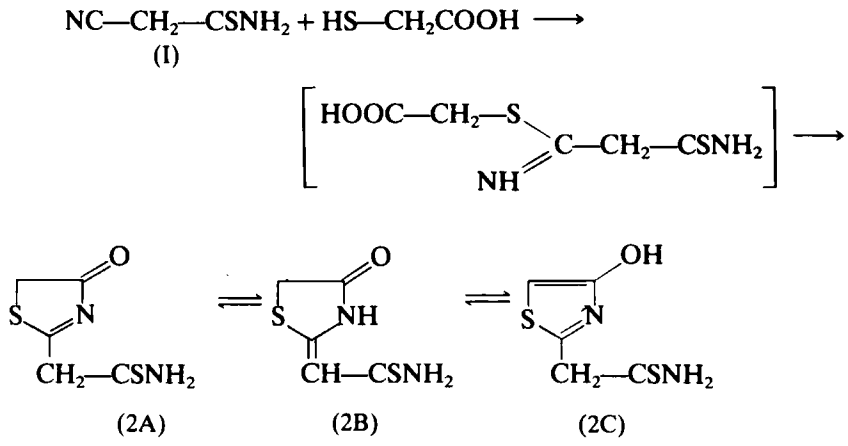
Treatment of α-cyanothioacetamide (**1**) with thioglycolic acid in pyridine led to the formation of 4-oxo-4,5-dihydro-1,3-thiazole-2-thioacetamide (**2**). (**2**) reacted with two equivalents of aryldiazonium chloride to afford the diarylazo derivatives (**3a–c**). However when (**2**) was reacted with an equivalent amount of aryldiazonium chloride the monoarylazo derivatives (**4a–c**) were obtained and not (**5a–c**), which can be prepared via the reaction of thioglycolic acid with α-arylazo-α-cyano-thioacetamide (**6a–c**). With aromatic aldehydes (**2**) reacted to give the diyildene derivatives (**7a–d**). The structures of the isolated products were established by elemental analyses, and spectral data studies.

INTRODUCTION

α-Cyanothioacetamide (**1**) is a versatile compound which has been utilised in heterocyclic synthesis. It is used extensively as a reactant since the methylene group, cyano group, thioxo group and amino group can take part in condensation reactions to give a variety of heterocyclic compounds.[1] As a part of our programme directed for development of new simple and efficient procedures for the synthesis of azoles of potential biological activity,[2–4] we report here a novel synthesis of a substituted thiazolinone via reaction of the readily accessible α-cyanothioacetamide or its azo derivatives with thioglycolic acid.

RESULTS AND DISCUSSION

When a mixture of (**1**) and thioglycolic acid was refluxed in pyridine, 4-oxo-4,5-dihydro-1,3-thiazole-2-thioacetamide (**2A**) or its possible tautomers (**2B**) or (**2C**) were obtained. The IR spectrum in the solid state shows that the product exists in the oxo from (**2A**), whereas in DMSO solution the hydroxy form (**2C**) predominates according to the ^{1}H-NMR spectrum (cf. experimental part).



(I) (2A) (2B) (2C)

The reaction between (**2**) and aryldiazonium chloride afforded mono-arylazo- or diarylazo derivatives depending on the ratio of the reactants. When (**2**) reacted with two equivalents of aryldiazonium chloride, the corresponding diarylazo derivatives (**3a–c**) were obtained in which coupling occurred at the two active methylene groups in (**2**). The reaction between (**2**) and aryldiazonium chloride in equimolecular amounts resulted in the formation of products corresponding to monoarylazo derivatives. The reaction products could be formulated as (**4a–c**) or their isomer (**5a–c**) or their tautomeric forms. Structure (**5**) was easily ruled out based on the nonidentify of the above products with those obtained by the action of thioglycolic acid on α-arylazo-α-cyanothioacetamide (**6a–c**)[5] (cf. Chart 1). This proves that structure (**4**) represents the products of reaction of (**2**) with equivalent amounts of aryldiazonium chloride. Moreover, when (**4a–c**) were reacted with aryldiazonium chloride, (**3a–c**) were obtained. On the other hand (**2**) reacted with aromatic aldehydes and the diylidene derivatives (**7a–e**) were the only isolable products. The structures of newly synthesised heterocyclic derivatives were established based on elemental analyses IR and ^{1}H-NMR spectral data studies.

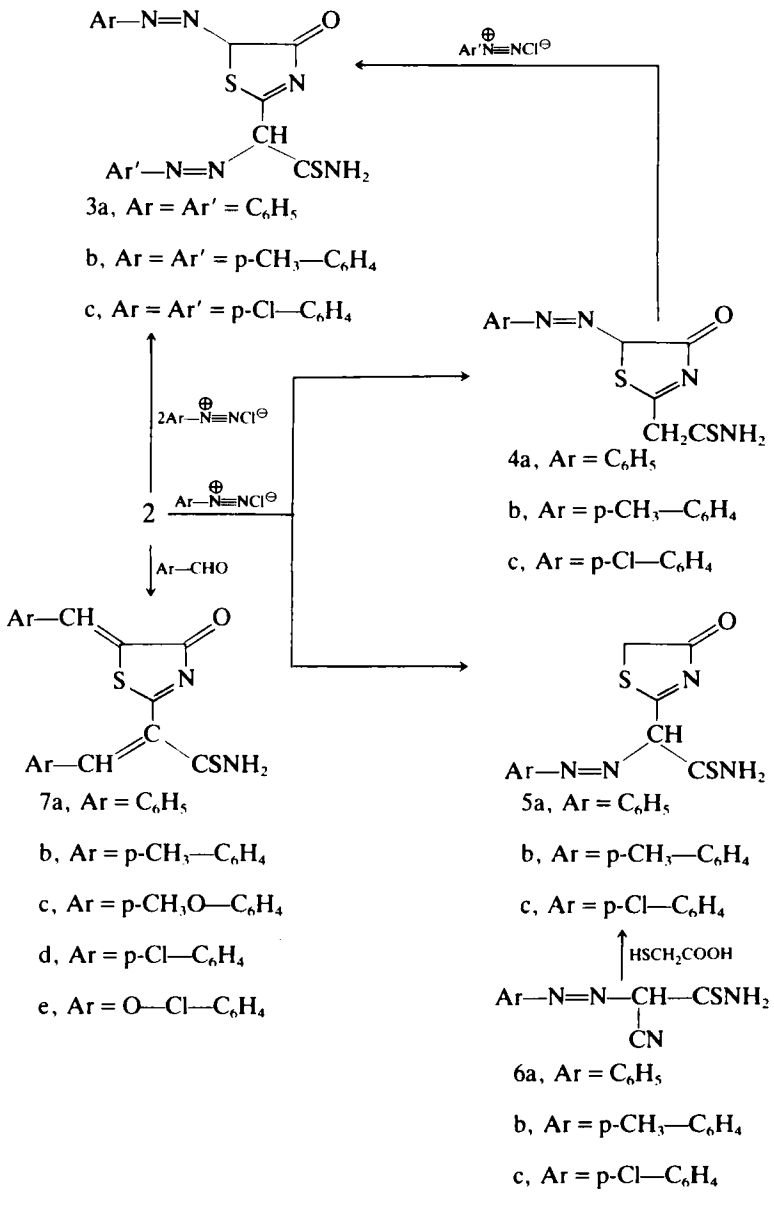
EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer in KBr discs. The ^{1}H-NMR spectra were recorded on a Varian EM 390-90 MHz spectrometer in deuterated DMSO-d_6 as a solvent and TMS as internal standard, chemical shifts are expressed as ppm units. Microanalytical data were performed by the Microanalytical Center at the Faculty of Science, Cairo University.

4-Oxo-4,5-dihydro-1,3-thiazole-2-thioacetamide (2). Mercaptoacetic acid (0.92 g, 0.01 mole) is added to a solution of α-cyanothioacetamide (1.0 g, 0.01 mole) in pyridine (24 ml) and the mixture is heated to reflux for 1 h. The solid precipitate obtained on cooling is isolated by suction and crystallized from DMF to give the colourless substance **2**, yield (70%), m.p. >3000°C.
Analysis: $C_5H_6N_2S_2O$ (174)

Calcd.:	C,	34.48;	H,	3.44;	N,	16.09;	S, 36.78
Found:	C,	34.2;	H,	3.2;	N,	16.4;	S, 36.5

IR (cm^{-1}); 3390, 3300 (NH_2); 1690 (ring C=O) and 1650 (C=N). ^{1}H-NMR (DMSO-d_6; δppm): =



3.5 (s, 2H, CH_2); 6.1 (s, 1H, 5-H); [8.4 (br, 2H, NH_2); 11.3 (s, 1H, OH) disappeared after D_2O exchange].

Preparation of diarylazo derivatives (**3a–c**) *from 4-oxo-4,5-dihydro-1,3-thiazole-2-thioacetamide* (2). A cold solution of (0.02 mole) of the appropriate diazotised aromatic amine (prepared from the equivalent amount of the amine, HCl and $NaNO_2$) was gradually added to a cold solution of **2** (1.74 g, 0.01 mole) in aqueous sodium hydroxide solution (2%, 20 ml) during 30 minutes at 0–5°C. The reaction mixture was kept in the ice-box for 2 hours with constant stirring. The solid product so formed was collected by filtration, washed with water then crystallised from ethanol to give red crystals **3a–c** (cf. Table I).

TABLE I

Characterization data of compounds **3a–c**, **4a–c** and **5a–c**

Compound	M.p. (°C)	Yield (%)	Mol. Formula	% Analysis Calcd./Found C	H	N	S	Cl	IR (cm^{-1})
3a*	185–6	70	$C_{17}H_{14}N_6S_2O$	53.40	3.66	21.98	16.75	—	3385, 3250 (NH_2), 1690 (ring C=O)
				53.7	3.5	22.2	16.4	—	and 1650 (C=N).
3b	150	75	$C_{19}H_{18}N_6S_2O$	55.6	4.39	20.48	15.6	—	3390, 3260 (NH_2); 1690 (ring C=O);
				55.3	4.6	20.7	15.2	—	and 1650 (C=N).
3c	192	72	$C_{17}H_{12}N_6S_2Cl_2O$	45.23	2.66	18.62	14.19	15.71	3400, 3290 (NH_2); 1695 (ring C=O);
				45.4	2.4	18.3	14.4	15.4	and 1650 (C=N).
4a	235–7	68	$C_{11}H_{10}N_4S_2O$	47.48	3.59	20.14	23.02	—	3380, 3210 (NH_2), 1700 (ring C=O);
				47.7	3.3	20.4	22.8	—	and 1655 (C=N).
4b	280–1	70	$C_{12}H_{12}N_4S_2O$	49.31	4.1	19.17	21.91	—	3370, 3190 (NH_2); 1700 (ring C=O);
				49.6	3.9	18.9	21.5	—	and 1650 (C=N).
4c	250–2	72	$C_{11}H_9N_4S_2OCl$	42.24	2.88	17.86	20.48	11.36	3400, 3310 (NH_2); 1700 (ring C=O);
				42.0	3.1	17.6	20.2	11.6	and 1655 (C=N).
5a	over 300	75	$C_{11}H_{10}N_4S_2O$	47.48	3.59	20.14	23.02	—	3380, 3300 (NH_2), 1690 (ring C=O);
				47.2	3.3	20.5	23.3	—	and 1645 (C=N).
5b	295–7	75	$C_{12}H_{12}N_4S_2O$	49.31	4.10	19.17	21.91	—	3370, 3290 (NH_2); 1690 (ring C=O);
				49.0	3.9	19.5	22.2	—	and 1640 (C=N).
5c	265–7	73	$C_{11}H_9N_4S_2OCl$	42.24	2.99	17.92	20.48	11.36	3390, 3300 (NH_2); 1695 (ring C=O);
				42.5	2.7	17.6	30.2	11.1	and 1660 (C=N).

* ^{1}H-NMR (DMSO-d_6), δppm): 3.6 (s, 1H, CH); 5.1 (s, 1H, 5-H); 7.3–7.6 (m, 10 H, ArH); 8.4 (br., 2H, NH_2 disappeared after D$_2$ change).

TABLE II

2-(1-Aminothiocarbonylstyryl)-5-benzylidene-4-oxo-4,5-dihydro-1,3-thiazole derivatives (**7a–c**).

Compound	M.p. (°C)	Yield (%)	Mol. Formula	% Analysis Calcd./Found C	H	N	S	Cl	IR (cm^{-1})
7a*	218–9	70	$C_{19}H_{14}N_2S_2O$	65.14	4.0	8.0	18.28	—	3380, 3290 (NH_2); 1690 (ring
				65.4	4.2	8.3	18.0	—	C=O) and 1650 (C=N).
7b	180	72	$C_{21}H_{18}N_2S_2O$	66.66	4.76	7.40	16.93	—	
				66.4	4.6	7.7	16.6	—	
7c	192–4	72	$C_{21}H_{18}N_2S_2O_3$	61.46	3.39	6.82	15.6	—	3390, 3290 (NH_2); 1690 (ring
				61.7	3.1	7.0	15.3	—	C=O); and 1660 (C=N).
7d	205–6	75	$C_{19}H_{12}N_2S_2OCl_2$	54.41	2.86	6.68	15.27	16.94	
				54.6	3.1	6.5	15.0	16.6	
7e	240–2	73	$C_{19}H_{12}N_2S_2OCl_2$	54.41	2.86	6.68	15.27	16.94	3400, 3310 (NH_2); 1700 (ring
				54.7	2.6	6.9	15.0	17.2	C=O) and 1665 (C=N).

• ^{1}H-NMR (DMSO-d_6: δppm); 6.5, 6.6 (2S, 2H, 2Ar-CH=); 7.3–7.8 (m, 10 H, ArH); 8.4 (br., 2H, NH_2 exchangeable with D_2O).

Compounds **3a–c** could also be obtained via initial coupling of **2** (0.01 mole) with the corresponding diazotised primary aromatic amines (0.01 mole) to yield **4a–c** respectively (cf. Table I). Compounds **4a–c** (0.01 mole) were then further coupled with the corresponding diazotised primary aromatic amines (0.01 mole) under the same experimental condition to give **3a–c** showing no depression in melting points and mixed melting points when admixed with samples of **3a–c** prepared as described above.

Reaction of α-arylazo-α-cyanothioacetamide derivatives (**6a–c**) *with mercapto acetic acid.* Mercaptoacetic acid (0.92 g, 0.01 mole) is added to a solution of α-arylazo-α-cyanothioacetamide derivatives (**6a–c**) (0.01 mole) in pyridine (30 ml) and the mixture is heated to reflux for 6 hours. The reaction mixture was left to cool at room temperature and poured onto ice cold water, then the solution was acidified with cold hydrochloric acid till complete precipitation. The products were collected by filtration and crystallised from ethanol to give **5a-c** (cf. Table I).

2-(1-*Aminothiocarbonylstyryl*)-5-*benzylidene*-4-*oxo*-4,5-*dihydro*-1,3-*thiazole* (**7a–e**). A mixture of compound **2** (1.74 g, 0.01) mole and sodium acetate (1 g) in acetic acid (25 ml) was treated with the appropriate aromatic aldehydes (0.011 mole) and heated under reflux for 3 hours. The major portion of the solvent was removed by distillation and the concentrated solution was then poured into excess of water. The solid separated was removed by filtration, washed well with water and dried in vacuum. It was then crystallised from ethanol to afford a brown crystalline product **7a–e** (cf. Table II).

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