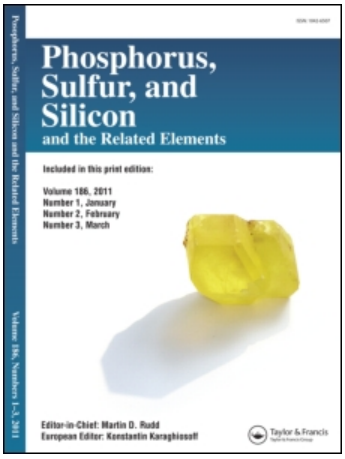

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REACTIONS WITH CYANOTHIOACETAMIDE DERIVATIVES: A NEW ROUTE FOR THE SYNTHESIS OF 2-THIAZOLIN-4-ONE THIAZOLO[4,5-*B*]PYRIDINE, THIAZOLINONYLPYRAZOLE AND PYRANO[2,3-*d*]-1,3-THIAZOLE DERIVATIVES

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REACTIONS WITH CYANOTHIOACETAMIDE DERIVATIVES: A NEW ROUTE FOR THE SYNTHESIS OF 2-THIAZOLIN-4-ONE, THIAZOLO[4,5-*b*]PYRIDINE, THIAZOLINONYLPYRAZOLE AND PYRANO[2,3-*d*]-1,3-THIAZOLE DERIVATIVES

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Several new 2-thiazolin-4-one, thiazolo[4,5-*b*]pyridine, thiazolin-4-on-2-yl pyrazole and pyrano[2,3-*d*]-1,3-thiazole derivatives were synthesised via the reactions of 2-α-cyanoacetonyl-2-thiazolin-4-one with a variety of α,β-unsaturated nitriles and other reagents. Structural elucidations were based on elementary analyses and spectral data studies.

Key words: Cyanothioacetamide; 2-thiazolin-4-ones; thiazolo[4,5-*b*]-pyridines; pyrano[2,3-*d*]-1,3-thiazoles; thiazolinonylpyrazoles.

INTRODUCTION

Cyanothioacetamide (**1**) and its derivatives are versatile reagents and their chemistry has gained a considerable recent attention.[1–4] As a continuation to our effort[5–8] directed for development of simple, new and efficient procedures for the synthesis of heterocycles with potential biological activities. We wish to report, here, the results of our investigation on the chemistry of 2-α-cyanoacetonyl-2-thiazolin-4-one (**3**). The reactions constitute a new route for the synthesis of several thiazole, thiazolinone, pyrazole and pyridine derivatives of expected biological activities.

RESULTS AND DISCUSSION

Thus, it has been found that α-acetyl-α-cyanothioacetamide (**2**, prepared by the action of acetyl chloride on cyanothioacetamide (**1**) in pyridine[9]) reacted with ethyl chloroacetate to afford a product of molecular formula $C_7H_6N_2SO_2$ corresponding to addition of one molecule of **2** to one molecule of the acetate followed by dehydrochlorination and the loss of one molecule of ethanol. The reaction product

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TABLE I

Characterization data of the newly synthesized derivatives

Comp.	Colour (Solvent)	M.P.	Yield	Mol. Formula	% Analysis		Calcd./Found	
					C	H	N	S
5a	Pale yellow (toluene)	257	73	$C_{17}H_{12}N_4SO_2$	60.7 60.9	3.6 3.7	16.7 16.4	9.5 9.3
5b	Golden yellow (toluene)	220	76	$C_{17}H_{11}N_3SO_3$	60.2 60.3	3.2 3.4	12.4 12.2	9.4 9.5
6a	Golden yellow (toluene)	215	70	$C_{17}H_{11}N_4SO_2$	60.9 61.0	3.3 3.4	16.7 16.5	9.5 9.3
6b	Yellow (toluene)	205	70	$C_{17}H_{11}N_4S_2O$	58.1 58.3	3.1 3.2	15.9 15.7	18.2 18.0
7	Yellow (toluene)	200	67	$C_{14}H_{10}N_2SO_2$	62.2 62.0	3.7 3.8	10.4 10.2	11.9 12.0
8	Orange (ethanol)	240	75	$C_{13}H_{10}N_4SO_2$	54.5 54.7	3.5 3.7	19.6 19.4	11.2 11.0
9a	Pale yellow (ethanol)	255	75	$C_7H_8N_4SO$	42.9 43.0	4.1 4.0	28.6 28.3	16.3 16.2
9b	Yellow (carbon-tetra-chloride)	215	70	$C_{13}H_{12}N_4SO$	57.4 57.3	4.4 4.2	20.6 20.3	11.8 11.6
11a	Yellow (toluene/ xylene)	220	70	$C_{14}H_{12}N_4SO$	59.2 59.4	4.2 4.3	19.7 19.5	11.3 11.1
11b	Yellow (toluene/ xylene)	200	65	$C_{20}H_{16}N_4SO$	66.7 66.8	4.4 4.2	15.6 15.4	8.9 8.7
12a	Yellow (carbon-tetra-chloride)	260	70	$C_{13}H_{12}N_6SO$	52.0 52.2	4.0 3.8	28.0 27.8	10.6 10.7
12b	Yellow (carbon-tetra-chloride)	245	65	$C_{19}H_{16}N_6SO$	60.6 60.3	4.3 4.1	22.3 22.1	8.5 8.7

could, however, be formulated as 2-α-cyanoacetonyl-2-thiazolin-4-one (**3**) on the basis of correct elemental analysis and spectral data. IR and ^{1}H-NMR spectral data were in a good agreement with the assigned structure. Compound **3** was taken as the starting material for the present study and its synthetic potential was demonstrated via its reactions with α,β-unsaturated nitrile derivatives and other reagents. Thus, it has been found that **3** reacted with α-cyanocinnamonitrile (**4a**) in *n*-butanol

in the presence of a catalytic amount of triethylamine to afford a product which could be formulated as the pyrano[2,3-*d*]-1,3-thiazole derivative **5a** on the basis of elemental and spectral data. The IR (cm^{-1}) spectrum of **5a** showed absorption bands related to the presence of NH_2 (3340, 3300), two CN (2220, 2200) and CO (1680) while its ^{1}H-NMR spectrum (δ ppm) revealed signals corresponding to the presence of CH_3CO (s, 2.7), pyran H-4 (s, 4.6) side chain—CH (6.3) and aromatic protons (m, 5H, 7.1–7.8). In the same manner, α-ethoxycarbonylcinnamonitrile (**4b**) reacted with **3** to yield the pyrano[2,3-*d*]-1,3-thiazole derivative **5b**. The IR spectrum of **5b** showed absorption bands for OH group at 3460 and one CO group at 1690 meaning that the enolate form is the most stable form rather than the keto-one (Experimental Part).

In contrast to the behavior of **3** toward **4a,b**, it reacted with the cinnamonitriles **4c,d** under practically the same experimental conditions to yield products which could be assigned the thiazolo[4,5-*b*]pyridine structure **6a,b** respectively on the

TABLE II
IR and ^{1}H-NMR data

Comp.	IR, KBr, cm^{-1}	^{1}H-NMR (DMSO-d_6), δ ppm
3	2980 (sat. CH and CH_2); 2220 (CN); 1710 (CO) and 1680 (CO).	2.7 (s, 3H, $COCH_3$); 5.6 (s, 2H, thiazoline-CH_2) and 6.2 (s, 1H, CH).
5a	3340, 3300 (NH_2); 2220 (CN); 2200 (CN); 1680 (CO) and 1250 (C-O-C).	2.7 (s, 3H, $COCH_3$); 4.6 (s, 1H, pyran H-4); 6.3 (s, 1H, CH); 7.1-7.8 (m, 5H, ArH's) and 9.8 (s, br, 2H. NH_2).
5b	3460 (OH); 2220 (CN); 2200 (CN); 1680 (CO) and 1260 (C-O-C).	2.8 (s, 3H, $COCH_3$); 4.7 (s, 1H, pyran H-4); 6.2 (s, 1H, CH); 7.0-7.7 (m, 5H, ArH's) and 10.8 (s, 1H, OH)
6a	3200 (NH); 2220 (CN); 2200 (CN); 1690 (CO); 1670 (CO) and 1630 (C=N).	2.8 (s, 3H, $COCH_3$); 6.3 (s, 1H, CH); 7.1-7.7 (m, 5H, ArH's) and 9.9 (s, br, 1H, NH).
6b	3250 (NH); 2220 (CN); 2200 (CN); 1680 (CO); 1540 (C=S) and 1630 (C=N).	2.75 (s, 3H, $COCH_3$); 6.3 (s, 1H, CH); 7.0-7.8 (m, 5H, ArH's) and 9.6 (s, br, 1H, NH).
7	2980 (sat. CH); 2220 (CN); 1710 (CO) and 1680 (CO).	2.7 (s, 3H, $COCH_3$); 6.2 (s, 1H, CH) and 7.2-7.9 (m, 6H, Ar and ylidenic protons).
8	3200 (NH); 3000 (sat CH); 2220 (CN); 1720 (CO); 1670 (CO) and 1620 (C=N).	2.7 (s, 3H, $COCH_3$); 6.2 (s, 1H, CH; 7.1-7.8 (m, 5H, ArH's) and 9.7 (s, br, 1H, NH).
9a	3350, 3300, 3200 (NH_2 and NH) and 1710 (CO).	2.75 (s, 3H, CH_3); 5.6 (s, 2H, thiazoline-CH_2); 9.6 (s, br, 1H, NH) and 9.9 (s, br, 2H, NH_2).
9b	3350, 3300 (NH_2) and 1710 (CO).	2.7 (s, 3H, CH_3); 5.7 (s, 2H, thiazoline-CH_2); 7.0-7.5 (m, 5H, ArH's) and 9.7 (s, br, 2H, NH_2).

TABLE II (*Continued*)

Comp.	IR, KBr, cm^{-1}	^{1}H-NMR (DMSO-d_6) δ ppm
10	3350, 3300, 3250 (NH_2 and NH); 2220 (CN) and 1270 (C-O-C).	2·8 (s, 3H, CH_3); 4·5 (s, 1H, pyran H-4); 7·1-7·7 (m, 5H, ArH's) and 9·8 (s, br, 5H, two NH_2 and NH).
11a	3400, 3350, 3250 (NH_2 and NH) and 1720 (CO).	2·7 (s, 3H, CH_3); 7·2-7·8 (m, 6H, phenyl and ylidene protons) and 9·6 (s, br, 3H, NH_2 and NH).
11b	3400, 3350 (NH_2) and 1710 (CO).	2·65 (s, 3H, CH_3); 7·0-7·6 (m, 11H, two phenyl and ylidene protons) and 9·7 (s, br, 2H, NH_2).
12a	3350, 3300, 3200 (NH_2 and NH) and 1720 (CO).	2·7 (s, 3H, CH_3); 7·1-7·7 (m, 5H, ArH's) and 9·75 (s, br, 4H, NH_2 and two NH).
12b	3340, 3300, 3190 (NH_2 and NH) and 1710 (CO).	2·8 (s, 3H, CH_3); 7·0-7·8 (m, 10 H, ArH's) and 9·6 (s, br, 3H, NH_2 and NH).

basis of elemental and spectral data. The IR spectra (cm^{-1}) of each of **6a,b** showed absorption bands corresponding to NH, two CN, two CO (or one CO and one C=S) indicating that the cyclization step involved the loss of one molecule of water rather than one molecule of ammonia. If it is the other way round, compound **4c** should had given **5b** as for **4b**. ^{1}H-NMR of both **6a,b** revealed signals for $COCH_3$, side chain-CH, aromatic and NH protons only in their proper places (Table II).

The reactivity of the cyclic CH_2 group in **3** was further demonstrated via its reactions with benzaldehyde and benzenediazonium chloride. Thus, **3** reacted with benzaldehyde and with benzenediazonium chloride to afford the corresponding 5-benzylidene- and 5-phenylhydrazo-2-thiazolin-4-one derivatives **7** and **8** respectively. The ^{1}H-NMR spectra of **7** and **8** revealed the absence of the singlet at 5.6 which corresponds to the cyclic CH_2 group in **3** and instead a singlet in the aromatic range (**7**) and a broad singlet for NH (**8**) were detected in the two spectra respectively (Table II). Moreover, **3** reacted with each of hydrazin hydrate and phenylhydrazine to give products which were formulated as the 4-(2-thiazolin-4'-on)-2'-ylpyrazole derivatives **9a,b** respectively. Structure of **9a,b** was based on elemental analyses and spectral data. IR spectra of **9a,b** showed the presence of one CO absorption band only at 1710 cm^{-1} indicating that the acetyl CO group was that involved in this reaction. The band related to the CN group was entirely absent in each case and thus proving the involvement of the nitrile function in the cyclization step.

In addition, **9a** reacted with **4a** to afford the pyrano[2,3-*d*]-1,3-thiazole derivative **10**. IR spectrum of **10** was in a good agreement with the assigned structure while its ^{1}H-NMR spectrum revealed among its signals that singlet at 4.5 (δ ppm) which is attributed to the presence of pyran H-4. A further proof for the structure of **10** was achieved via its synthesis through another route by the reaction of **5a** with hydrazine hydrate in an excellent yield.

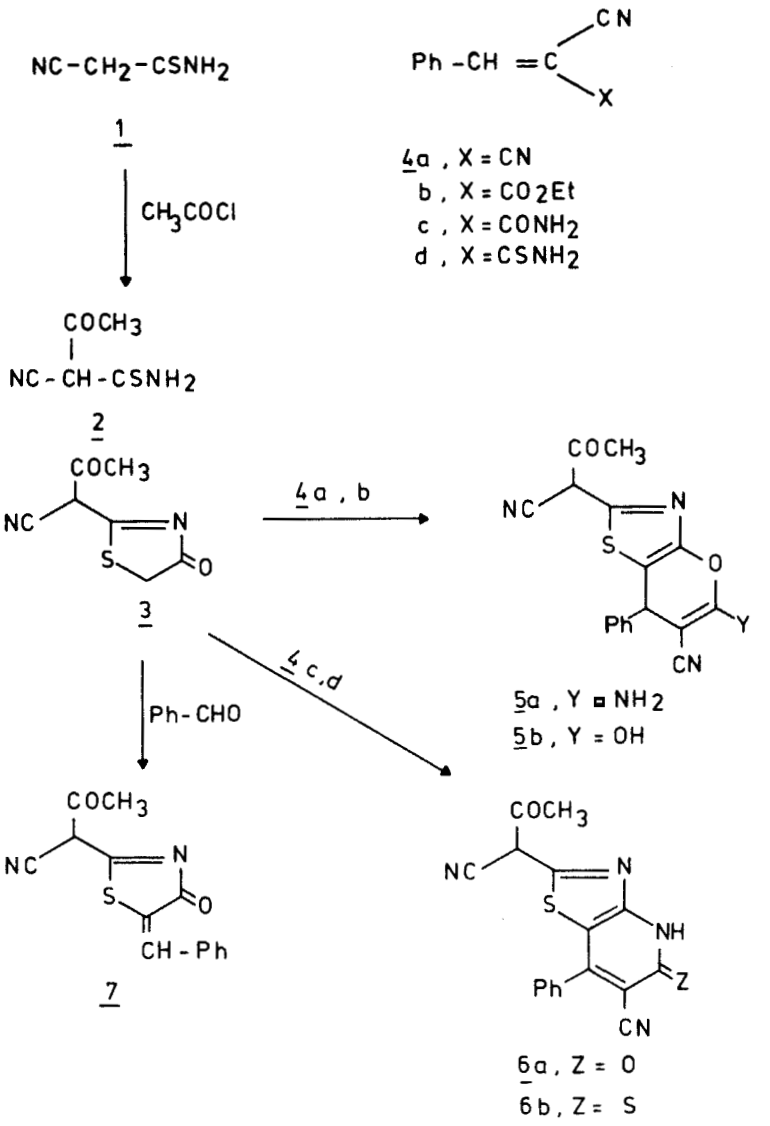

CHART I

Furthermore, each of **9a,b** reacted with benzaldehyde and with benzene-diazonium chloride to afford products which were formulated as the 5-benzylidene- and 5-phenylhydrazo-2-thiazolin-4-one derivatives **11a,b** and **12a,b** respectively. Structures **11a,b** and **12a,b** were established by elemental analyses, IR and ^{1}H-NMR spectral data studies which were found in a good agreement with the assigned structures (Table II). Compound **11a** could also be synthesised via the reaction of **7** with hydrazine hydrate while **12a** was synthesised also by the reaction of the same reagent with **8**.

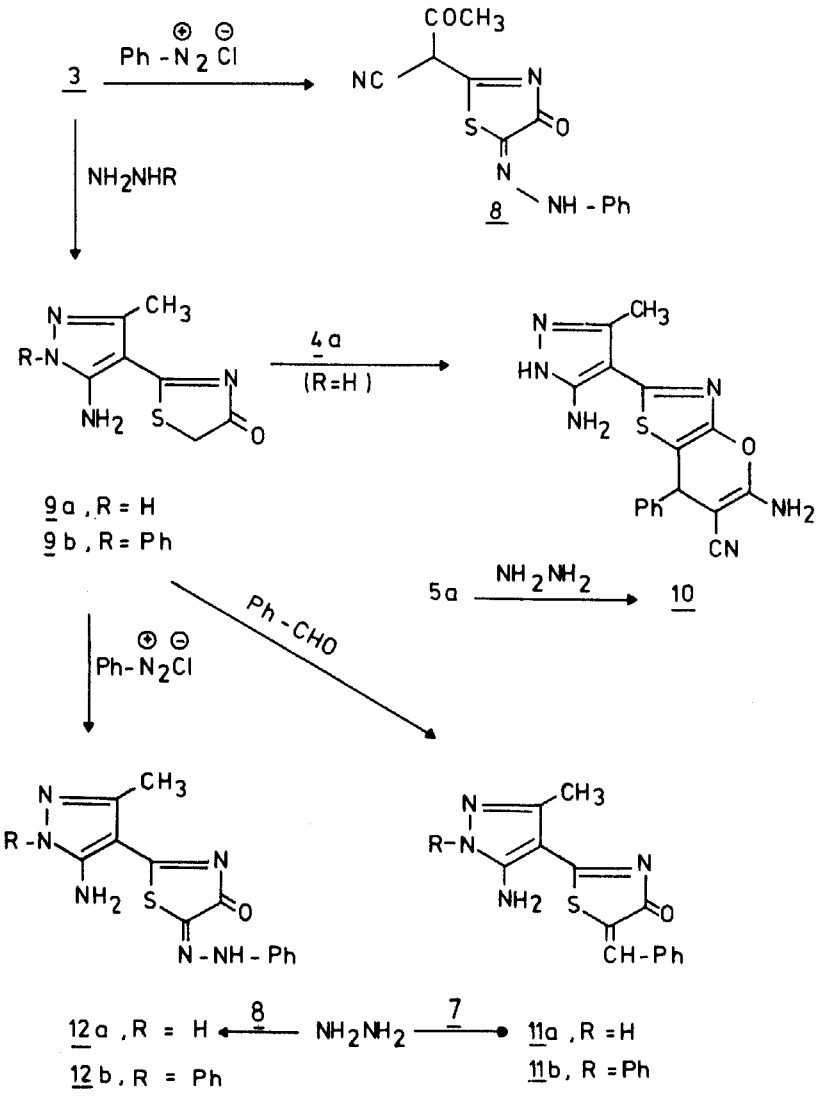

CHART II

EXPERIMENTAL

All melting points are uncorrected. IR (KBr) were recorded on a Pye Unicam SP. 1100 spectrometer. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Varian EM 390 90 MHz spectrometer using TMS as an internal standard and chemical shifts are expressed as δ ppm units. The microanalyses were performed at the Microanalytical Center of Cairo University using Perkin-Elmer 2400 CHN Analyzer. Compounds **1**,[10] **2**[9] and **4a–d**[11,12] were prepared following literature procedures.

Reaction of α-acetyl-α-cyanothioacetamide (**2**) *with ethyl chloroacetate.* A solution of **2** (0.01 mole) in absolute ethanol (30 ml) was treated with ethyl chloroacetate (0.01 mole) and sodium ethoxide solution. The reaction mixture was heated under reflux for 1 h poured onto cold dil. hydrochloric acid. The solid

product obtained after cooling was filtered off and crystallized from the proper solvent to give **3** (Tables I and II).

General procedure for the reaction of each of **3** *and* **9a** *with* **4a–d**. A solution of each of **3** or **9a** (0.01 mole) in *n*-butanol (30 ml) containing triethylamine (0.5 ml) was treated with each of **4a–d** (0.01 mol) and the whole was heated under reflux for 4–6 h. The solid products obtained after cooling or while the solution was still boiling were filtered off and crystallized from the proper solvents to give **5a,b 6a,b** and **10** respectively (Tables I and II).

General procedure for the reaction of each of **3** *and* **9a,b** *with benzaldehyde*. A solution of equimolecular (0.01 mole) amounts of each of **3** or **9a,b** and benzaldehyde in *n*-butanol (30 ml) was heated under reflux for 5 h. The solid products which separated after cooling were filtered off and crystallized from the proper solvents to give **7** and **11a,b** respectively (Tables I and II).

General procedure for the reaction of **3** *and* **9a,b** *with benzenediazonium chloride*. A very cold solution of 0.01 mole of benzenediazonium chloride (prepared from the equivalent amounts of aniline, HCl and $NaNO_2$) was gradually added to a cold solution of each of **3** or **9a,b** (0.01 mol) in *n*-butanol (30 ml) during 30 min. The reaction mixture was then kept in the ice-chest for 2 h with constant stirring. The solid product so formed was collected, washed with water then crystallized from the proper solvent to give **8** and **12a,b** respectively (Tables I and II).

General procedure for the reaction of **3, 5a, 7** *and* **8**. A solution of each of **3, 5a, 7** or **8** (0.01 mol) in ethanol (30 ml) was treated with each of hydrazine hydrate or phenylhydrazine (0.01 mol) and the reaction mixture was then heated under reflux for 5 h. The solid products obtained after cooling were collected by filtration and crystallized from the proper solvents to give **9a,b, 10, 11a** and **12a** respectively (Tables I and II).

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