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New Syntheses of Thiazole and Thiophene Derivatives

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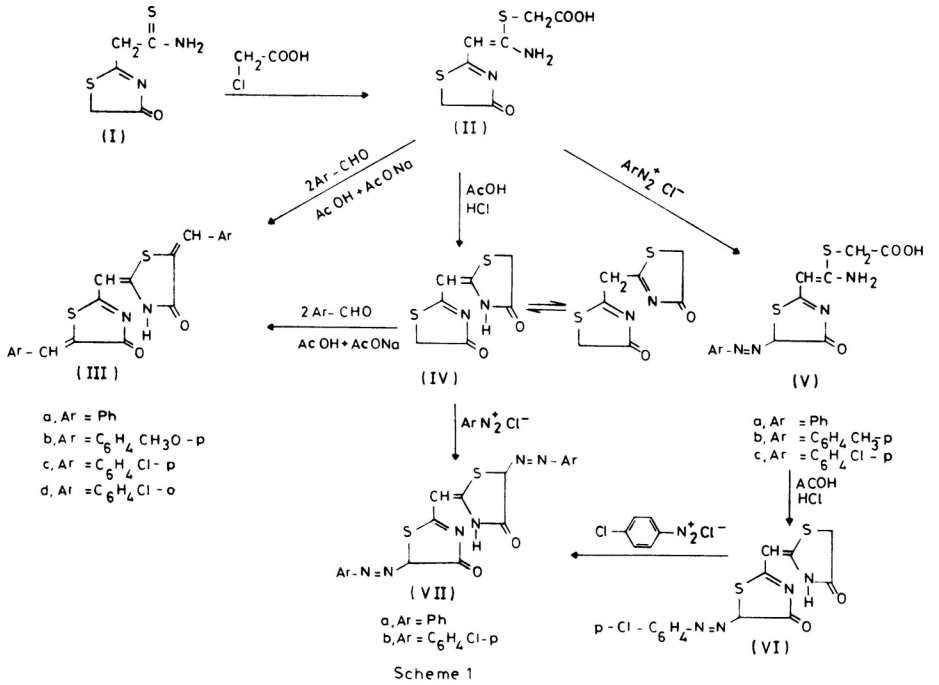
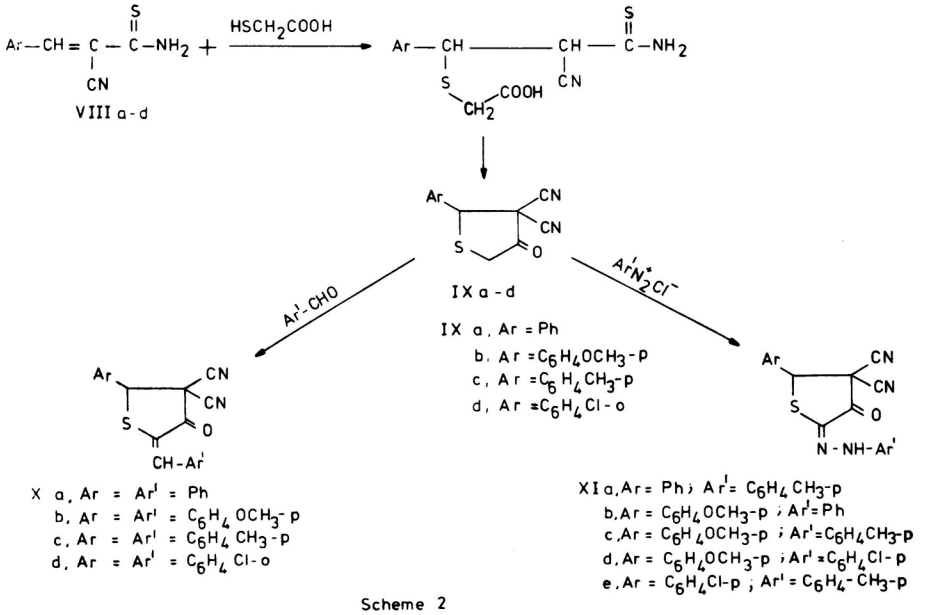
A novel synthesis of methylenebis(Δ^2-1,3-thiazoline-4-one) via reaction of chloroacetic acid with (Δ^2-1,3-thiazoline-4-one-2-yl)thioacetamide and a new route for synthesis of 2-aryl-4-oxothiolane-3,3-dicarbonitrile via the reaction of thioglycolic acid with 3-aryl-2-cyanothioacrylamides are reported. The reaction of aromatic aldehydes and arenediazonium chloride with active methylene compounds is discussed. The structures of all new compounds are established and the mechanism proposed for some reactions.

Biological activity and industrial importance of thiazoles prompted interest in the synthesis of several new thiazole derivatives.[1-3] In a previous work, we reported several new and efficient approaches to azoles utilizing easily available starting compounds.[4,5] In a recent paper,[6] we reported new synthesis for (Δ^2-1,3-thiazoline-4-one-2-yl)thioacetamide (I) from α-cyanothioacetamide and thioglycolic caid. This paper deals with I as starting material for the synthesis of new thiazole derivatives. It has been found that I with chloroacetic acid in the presence of sodium hydroxide yields II. The structure of II was assigned on the basis of elemental analysis, IR and ^{1}H NMR data (cf. experimental part). Reaction of II with appropriate aromatic aldehydes in the presence of acetic acid and anhydrous sodium acetate afforded IIIa-d. Compounds IIIa-d were also prepared by cyclization of II in a mixture of glacial acetic acid and conc. hydrochloric acid to give the known compound 2,2^1-methylenebis(Δ^2-1,3-thiazoline-4-one) IV.[7] Condenzation of IV with aromatic aldehydes afforded III (cf. Scheme I). On the other hand, II and IV react with arenediazonium chloride to give the monoarylazo and diarylazo derivatives Va-c and VIIa,b, respectively. Compound VIIb can be prepared by refluxing of Vc in a mixture of acetic acid-hydrochloric acid, providing the cyclized product VI, which in turn couples with 4-chlorobenzenediazonium chloride to give VIIb.



Scheme 1



Scheme 2

The present study is extended to the reaction of 3-aryl-2-cyanothioacrylamide VIIIa-d with thioglycolic acid. It has been found that in pyridine the addition of one mole of VIII to one mole of thioglycolic acid, with elimination of one mole of water and one mole of hydrogen sulphide, affords 2-aryl-4-oxothiolane-3,3-dicarbonitrile IXa-d. Formation of IX is assumed to proceed via initial addition of the mercapto group of thioglycolic acid to the double bond in VIII. The Michael adduct may then cyclize by loss of H_2O, followed by elimination of H_2S or elimination of H_2S followed by cyclization by loss of H_2O (cf. Scheme 2). The IXa structuer was confirmed by comparison with the previously prepared sample.[7] Compounds IXa-d condensed readily with aromatic aldehydes to give the corresponding arylidene derivatives Xa-d, and reacted with aryldiazonium chloride to afford XIa-e, which exist in the hydrazo rather than in the azo form (cf. Experimental).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded for KBr pellets on a Pye Unicam SP-1000. ^1H NMR spectra were obtained on an EM-90 MHz spectrometer in DMSO using TMS as internal standard. Chemical shifts are expressed as ppm. Elemental analyses were performed on the microanalytical data Unit at Cairo University.

Action of chloroacetic acid on (Δ²-1,3-thiazoline-4-one-2-yl)thioacetamide. To 0.01 mol of 1, dissolved in a mixture of 2% aqueous sodium hydroxide (40 ml) and ethanol (40 ml), chloroacetic acid (0.01 mol) was added, and reaction mixture was refluxed on a steam bath for 3 hrs. The solid product which separated from the boiling reaction mixture was filtered off, washed with water, dried and recrystallized from DMF to give brown crystals m. p. 285 °C, yield 70%.

Anal. for $C_7H_8N_2S_2O_3$ Calcd.: C 36.20; H 3.44; N 12.06; S 27.58
Found: C 36.5; H 3.2; N 12.3; S 27.4

IR (cm^{-1}): 3400, 3280 (NH_2); 2400—3400 (broad OH); 1720, 1700 (2C = O); 1645 (C = N). ^1H NMR: 3.5, 4.2 (2s, $2CH_2$); 6.2 (s, 1H, CH = C); 8.6 (s, 2H, NH_2); 11.4 (s, 1*H*).

Synthesis of Diarylidene Derivatives IIIa-d

Method A. A mixture of compound II (0.005 mol, 1.16 g), fused sodium acetate (2.5 g) and a slight excess (0.0055 mol) of the appropriate aromatic aldehyde was refluxed for 2 hours in 25 ml glacial acetic acid. The reaction mixture was cooled, poured over cold water, the separated solid was filtered off, washed with water and recrystallized from ethyl alcohol to give brown coloured products IIIa-d (cf. Table I).

Method B. Compounds IIIa-d were prepared by condensation of IV (0.005 mol) with the appropriate aromatic aldehydes (0.0055 mol) in acetic acid (25 ml) in the presence of sodium acetate (2.5 g), using the same conditions as in method A. They exhibited the same analytical and spectral data.

Action of concentrated hydrochloric acid on II. A mixture of 1 g of II and 20 ml of concentrated hydrochloric acid and 30 ml acetic acid was refluxed for 1 h. The reaction mixture was allowed to cool and the separated solid was collected by filteration. It was crystallized from glacial acetic acid as IV m. p. 225 °C (yield 75%) not depressed with the authentic sample.[7]

Cyclization of Vc. A mixture of 1 g of Vc. 20 ml of concentrated hydrochloric acid and 30 ml of acetic acid was refluxed for 3 hns. The reaction mixture was allowed to cool, the solid was collected by filteration. It was crystallized from dioxane affording the reddish brown product VI, m. p. 290 °C (yield 70%).

Anal. $C_{13}H_9N_4S_2O_2Cl_2$ Calcd.: C 44.25; H 2.55; N 15.88; S 18.15; Cl 10.07
Found: C 44.1; H 2.8; N 15.7; S 18.0; Cl 10.2

IR (cm^{-1}): 3400 (NH), 1720, 1710 (2C = O) and 1640 (C = N). ^1H NMR: 4.2 (s, 2H, CH_2); 4.7 (s, 1H, CH); 6.4 (s, 1H, CH = C); 7.3-7.6 (m, 4H, Ar-*H*) and 9.6 (s, 1H, N*H*).

TABLE I

The characterization data of the arylidene derivatives IIIa-d and arylazo compounds Va-c.

Compound	M.P. °C	Yiled %	Formula	Analysis calcd. / Found C %	H %	N %	S %	Cl %	IR/cm^{-1}	^{1}H-NMR/ppm
IIIa	214	70	$C_{21}H_4N_2O_2S_2$	64.61 64.9	3.58 3.4	7.17 7.0	16.41 16.5	— —	3330 (NH); 1720 1710 (2C=O) and 1640 (C=N)	6.2 (s, 1H, CH=C); 6.7 (s, 2H, 2C=CHAr), 7.4-7.7 (m, 10 H, Ar-*H*) and 10.3 (s, 1H, NH exchangeable with D_2O).
IIIb	224-5	72	$C_{23}H_{18}N_2O_4S_2$	61.33 61.5	4.0 4.3	6.22 6.5	14.22 14.0	— —	3340 (NH); 1720 1710 (2C=O) and 1645 (C=N)	3.9 (s, 6H, 2 OCH_3); 6.4 (s, 1H, CH=C); 6.7 (s, 2H, 2C=CH-Ar), 7.3-7.7 (m, 8H, Ar-*H*) and 10.5 (s, 1H, NH).
IIIc	280	75	$C_{21}H_{21}N_2O_2S_2Cl_2$	54.90 54.7	2.61 2.5	6.10 6.3	13.94 13.7	15.46 15.6	3340 (NH); 1710 1700 (2C=O) and 1645 (C=N)	2H, 2C=CH-Ar); 7.4-7.8 (m, 8H, Ar-*H*) and 10.8 (s, 1H, NH).
IIId	250-1	74	$C_{21}H_{12}N_2O_2S_2Cl_2$	54.9 55.2	2.61 2.4	6.10 5.8	13.94 13.7	15.46 15.3		
Va	180	75	$C_3H_{12}N_4O_3S_2$	46.42 46.6	3.57 3.4	16.66 16.5	19.04 18.8	— —	3380, 3290 (NH_2); 3400-2400 (broad OH); 1720, 1700 (2C=O) and 1635 (C=N).	3.5 (s, 2H, CH_2);4.2 (s, 1H, CH); 6.3 (s,1H, CH=C); and [8.5 (s, 2H, NH_2);11.3 (s, 1H, COOH exchangeable with D_2O].
Vb	260	70	$C_{14}H_{14}N_4O_3S_2$	48.0 48.3	4.0 4.2	16.0 16.1	18.28 18.5	— —	3360, 3280 (NH_2); 3400-2400 (broad OH); 1720, 1700 (2 C=O)	2.2 (s, 3H, CH_3); 3.5 (s, 2H, CH_2); 4.0 (s, 1H, CH); 6.3 (s, 1H, CH=C); 7.2-7.4 (m, 4H, Ar-*H*); 8.4 (s, 2H, NH_2) and 11.2 (s, 1H, COOH).
Vc	230	72	$C_{13}H_{11}N_4O_3S_2Cl$	42.1 42.0	2.96 3.1	15.11 15.0	17.27 17.5	9.58 9.4	and 1630 (C=N). 3380, 3300 (NH_2); 34-2400 (broad OH), and 1640 (C=N).	3.6 (s, 2H, CH_2); 4.2 (s, 1H, CH=C), 7.3-7.5 (m, 4H, Ar-*H*), 8.5 (s, 2H, NH_2) and 11.5 (s, 1H, COOH).

TABLE II

2-Aryl-4-otothiolane-3,3-dicarbonitrile IXb-d

Compound	M. P. °C	Yield %	Formula	Analysis Cald. / Found C %	H %	N %	S %	Cl %	IR [com^{-1}]	^{1}H-IMR [ppm]
IXb	250	74	$C_{13}H_{10}N_2O_2S$	60.46 60.7	3.87 3.5	10.85 11.0	12.4 12.2	— —	2220, 2200 (2 CN) and 1730 (C=O)	3.7 (s, 3H, OCH_3); 4.1 (s, 1H, CH); 4.5 (s, 2H, CH_2) and 7.4-7.6 (m, 4H, Ar-*H*).
IXc	285-7	70	$C_{13}H_{10}N_2OS$	64.46 64.2	4.13 4.4	11.57 11.4	13.22 13.0	— —	2210, 2200 (2 CN) and 1720 (C=O).	2.3 (s, 3H, CH_3); 4.0 (s, 1H, CH); 4.3 (s, 2H, CH_2) and 7.2-7.4 (m, 4H, Ar-*H*).
IXd	225	76	$C_{12}H_7OSCl$	54.85 55.0	2.66 2.5	10.66 10.9	12.19 12.0	13.52 13.3	2220, 2200 (2 CN) and 1730 (C=O).	4.1 (s, 1H, CH), 4.5 (s, 2H, CH_2) and 7.3-7.5 m, 4H, Ar-*H*).

TABLE III

The characterization data of the arylidene derivatives Xa-d and arylazo compounds XIa-e

	M. P. °C	Yield %	Formula	Analysis Cald. / Found C %	H %	N %	S %	Cl %	IR/cm^{-1}	^{1}H-NMRδ/ppm
Xa	190	70	$C_{19}H_{12}N_2OS$	72.2 72.5	3.79 4.1	8.86 8.6	10.12 10.4	— —	2220, 2200 (2CN) and 1720 (C=O)	4.0 (s, 1H, CH); 6.7 (s, 1H, C=CH-Ar) and 7.2-7.5 (m, 10 H, Ar-*H*).
Xb	160	76	$C_{21}H_{16}N_2O_3S$	67.02 67.2	4.25 4.0	7.44 7.6	8.51 8.3	— —	2230, 2210 (2 CN) and 1730 (C=O).	
Xc	212-3	75	$C_{21}H_{16}N_2OS$	73.25 73.0	4.65 4.5	8.13 8.0	9.30 9.5	— —	2220, 2200 (2 CN) and 1720 (C=O).	2.3 (s, 6H, $2CH_3$); 4.0 (s, 1H, CH); 6.5 (s, 1H, C=CH-Ar) and 7.2-7.7 (m, 8H, Ar-*H*).
Xd	240	70	$C_{19}H_{10}N_2OSCl_2$	59.22 59.5	2.59 2.8	7.27 7.5	8.31 8.2	18.44 18.6	2220, 2210 (2 CN) and 1720 (C=O).	4.1 (s, 1H, CH); 6.6 (s, 1H, C=CH-Ar) and 7.3-7.7 (m, 8H, Ar-*H*).

Reaction of II with diazotized aromatic amines. A cold solution of 0.01 mol of diazotized aromatic amine was gradually added to a cold solution af II (0.01 mol) dissolved in aqueous sodium hydroxide (2%, 20 ml) over 15 minutes at 0-5 °C. The reaction mixture was stirred in the ice-box for 2 hrs. The solid product was collected by filtration, washed with water, then crystallized from ethanol to give brown products Va-c (cf. Table I).

Action of p-chlorobenzenediazonium chloride on VI. Compound VI (0.01 mol) was coupled with 4-chlorobenzenediazonium chloride (0.01 mol) under the above conditions. The reaction product was crystallized from dioxane to give the reddish brown substance VIIb, m. p. 270 °C (yield 65%).

Anal. $C_{19}H_{12}N_6O_2S_2Cl_2$ Calcd.: C 46.43; H 2.44; N 17.10; S 13.03; Cl 14.46

Found: C 46.3; H 2.2; N 17.3; S 13.3; Cl 14.6

IR (cm^{-1}): 3390 (NH); 1720, 1710 (2 C = O) and 1640 (C = N). ^1H NMR: 4.8 (s, 2H, 2C*H*); 6.4 (s, 1H, C*H* = C); 7.3-7.6 (m, 8H, Ar-*H*) and 10.2 (s, 1H, N*H*).

Action of aryldiazonium chloride on IV. Compound IV (0.01 mol) was coupled with the corresponding diazotized primary aromatic amine (0.02 mol) under the above experimental conditions. Reaction products were crystallized either from ethanol (VII a) or dioxane (VII b) to give reddish brown crystals.
VII a, m. p. 195 °C (yield 70%).

Anal. $C_{19}H_{14}N_6O_2S_2$ Calcd.: C 54.02; H 3.31; N 19.9; S 15.16

Found: C 54.3; H 3.5; N 19.6; S 15.0

IR (cm^{-1}): 3370 (NH); 1710, 1700 (2 C = O) and 1640 (C = N).
Compound VII b prepared by this route was identical (m. p., mixed m. p., analytical and spectral data) with VII b prepared from VI.

Reaction of 3-aryl-2-cyanothioacrylamides (VIII a-d) with thioglycolic acid. Thioglycolic acid (0.92 g, 0.01 mol) is added to a solution of 3-aryl-2-cyanothioacrylamide derivatives (VIII a-d) (0.01 mol) in pyridine (30 ml) and the mixture is heated under reflux for 6 hrs. Reaction mixture was cooled to room temperature, poured over ice cold water, the solution was acidified with hydrochloric acid to complete the precipitation. Crude products were collected and crystallized from ethanol to give brown substances IX a-d (cf. Table II).

Reaction of IX a-d with aromatic aldehydes. Solution of IX a-d (0.01 mol) in acetic acid (20 ml) and sodium acetate (1 g) and aromatic aldehyde (0.01 mol), was heated under reflux for 2 hrs. The solid product separated while the reaction mixture was still boiling. They were filtered off, washed with water, dried and recrystallized from ethanol affording yellow crystals of X a-d (cf. Table III).

Reaction of IX a-c with diazotized aromatic amines. Compounds IX a-c (0.01 mol) were coupled with diazotized primary aromatic amine (0.01 mol) under the same experimental conditions as described for preparation of V a-c. Crude products were crystallized from ethanol affording brown crystals of XI a-e (cf. Table III).

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SAŽETAK

Nove sinteze tiazolskih i tiofenskih derivata

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Reakcijom kloracetatne kiseline s Δ^2-1,3-tiazolin-4-on-2-il)tioacetamidom pripravljen je metilenbis(Δ^2-1,3-tiazolin-4-on), a reakcijom glikolne kiseline s 3-aril--2-cijanotiakrilamidima priređeni su 2-aril-4-oxotiolan-3,3-dikarbonitrili. Određena je struktura novih spojeva i opsan mehanzam reakcja.