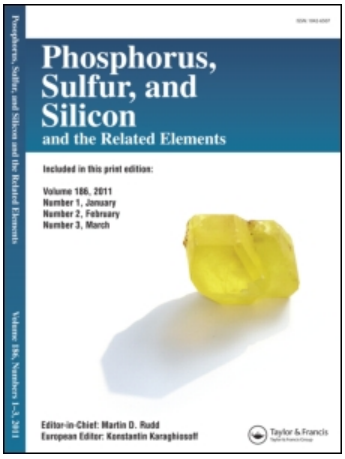

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A Facile Synthesis of New Unsymmetrical Azines by Cyclodesulfurization Reactions of Dithioesters with Diamines

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A FACILE SYNTHESIS OF NEW UNSYMMETRICAL AZINES BY CYCLODESULFURIZATION REACTIONS OF DITHIOESTERS WITH DIAMINES

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Dithioesters **2a, b** were prepared and methylated to give dimethyl thioesters **3a, b**. Azines **4a–d** and **5a, b** were obtained in one step from **2** with primary diamines or in two steps through **3**. Dithioesters **2a, b** reacted with amines in ethanol to produce thiosemicarbazones **6a, b** and **8a–d**, while in butanol reacted with morpholine to form **7a, b**.

Key words: Azines, dithioester, hydrazinecarbodithioate, imidazoles, pyrimidines, thiosemicarbazones.

Unsymmetrical azines have been realized with their applications and uses as tumors inhibitor,[1,2] antimalarial agents,[3,4] fluorescent brightening agents and photosensitizers.[5,6] Beside the uses of sulphonamides as bacteriostasis and fungistasis agents.[7,8]

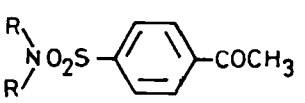
Different methods for preparation of unsymmetrical azines have been reported[1,9,10] which required multiple stages. Recently, Lin and Klayman[11] recorded a new synthetic method of unsymmetrical azines by the interaction of methyl arylalkylidenehydrazinecarbodithioates with diamines.

This work was devoted to investigate the influence of the sulphamido moiety on the preparation of new unsymmetrical azines. Thus a new and facile synthesis of unsymmetrical azines were carried out by the treatment of dimethyl 1-arylethylidenehydrazinecarbodithioates **3a, b** with available primary diamines.

The synthesis of **3a, b** was achieved by the condensation of methyl hydrazinecarbodithioate[12] with acetophenone derivatives **1a, b**[13] to give dithioesters **2a, b** followed by methylation with dimethyl sulphate. The resulting dimethyl thioester **3a** or **3b** was then refluxed with excess of primary diamine without solvent for about 10 hours. Under these conditions, ethylene diamine, 1,2-propanediamine or 1,3-propanediamine reacted smoothly with **3a, b** to give good yields of 2-substituted-4,5-dihydroimidazoles **4a–d** and 2-substituted-4,5,6-trihydropyrimidines **5a, b** through the evolution of methyl mercaptan. The mechanism of this reaction is similar to that reported earlier.[11]

Azines **4** and **5** were also prepared from the reaction of **2a, b** with requisite diamines by fusion or in ethanol as a medium. However, this result (closed structure) contradicts with the one recorded by Lin and Klayman[11] in which the mono- and bis-thiosemicarbazones (open structure) were obtained by the reaction of dithioesters with primary diamines.

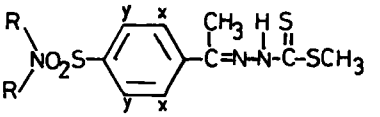
The formation of azines **4** and **5** from **2** proceed through concomitant evolution of methyl mercaptan and hydrogen sulphide and the mechanism of this reaction



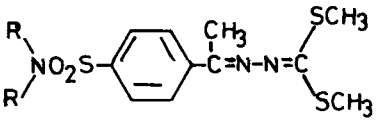
1

a, R = CH_3

b, R = CH_2CH_3



2



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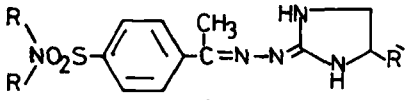


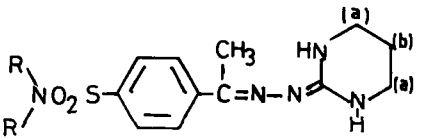
4

a, R = CH_3 ; R' = H

b, R = CH_3 ; R' = CH_3

c, R = CH_2CH_3 ; R' = H

d, R = CH_2CH_3 ; R' = CH_3



5

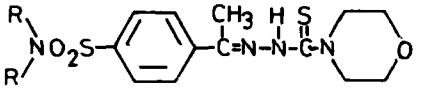
a, R = CH_3

b, R = CH_2CH_3

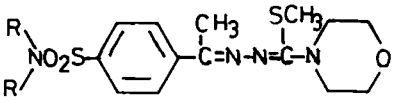
has been described by Lin and Klayman,[11] through the formation of thiosemicarbazone. Unfortunately, all attempts to separate the thiosemicarbazone failed.

It should be mentioned that the yields of azines **4** and **5** obtained from **2** and **3** [two steps] are somewhat higher than that obtained from **2** directly [one step].

Interaction of morpholine on dithioesters **2a, b** in boiling ethanol gave the corresponding thiosemicarbazones **6a, b** through evolution of methyl mercaptan while in boiling *n*-butanol evolution of hydrogen sulphide was perceived and **7a, b** were obtained.



6

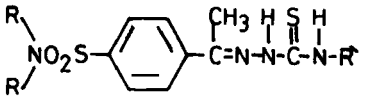


7

a, R = CH_3

b, R = CH_2CH_3

The structure of compounds **6** and **7** has been confirmed in part due to the positive and negative results respectively of the Turkevich and Makukha reaction[14] specific for aminothione (S=C—NH—). In the other part, due to the stretching



8

a, $R = CH_3$; $\hat{R} = CH_2CH_2CH_3$

b, $R = CH_3$; $\hat{R} = CH_2C_6H_5$

c, $R = CH_2CH_3$; $\hat{R} = CH_2CH_2CH_3$

d, $R = CH_2CH_3$; $\hat{R} = CH_2C_6H_5$

mode of the NH band observed at 3200 cm^{-1} in the mid-infrared spectra of **6** and the disappearance of the same vibration in the mid-infrared spectra of **7**.

However reaction of *n*-propylamine or benzylamine with **2a, b** afforded the desired thiosemicarbazones **8a–d**.

EXPERIMENTAL

Melting points were taken on Griffin melting point apparatus and are uncorrected. Infrared spectra of solid samples were run as KBr discs on a Shimadzu model 440 spectrophotometer. ^{1}HNMR spectra were measured in $CDCl_3$ or DMSO-d_6 using Fx 90Q Fourier Transform ^{1}HNMR. Mass spectra were performed using Shimadzu-GC. MS-QP 1000 EX using the direct inlet system. Analytical data were performed in Micro-analytical Center at Cairo University.

Preparation of Dithioesters **2a, b**

A mixture of acetophenone derivative[13] (**1a** or **1b**: 0.01 mole) and methyl hydrazinecarbodithioate[12] (0.01 mole) in methanol (50 ml) was heated under reflux for 3 h. After cooling, the crystals were collected and recrystallized from ethanol to give **2a, b** (Table I).

IR of **2a**: ν 3350 cm^{-1} (NH), ν 1580 cm^{-1} (C=N), ν 1250 cm^{-1} (C=S), ^{1}HNNR of **2a** (DMSO-d_6): δ 2.55 (s, 3H; CH_3—C=N), δ 2.65 (s, 3H; SCH_3), δ 2.8 (s, 6H; $N(CH_3)_2$), δ 7.8 (s, 1H; NH), δ 8.2 (d, 2H, ArH_x), δ 8.5 (d, 2H, ArH_y).

Methylation of Dithioesters **2a, b**

To the rapidly stirred suspension of dithioester (**2a** or **2b**; 0.1 mole) in 10% NaOH (25 ml), dimethyl sulphate (0.15 mole) was added. The separated solid was filtered off, washed with water and recrystallized from methanol to give the corresponding dimethyl derivatives **3a, b** (Table I).

IR of **3a, b**: ν 1590 cm^{-1} (C=N), ^{1}H NNR of **3a** ($CDCl_3$): δ 2.55 (s, 3H; CH_3—C=N), δ 2.60 and δ 2.65 (s, 6H; $C(SCH_3)_2$), δ 2.8 (s, 6H; $N(CH_3)_2$), δ 8.2 (d, 2H, ArH_x), δ 8.5 (d, 2H, ArH_y).

Preparation of Azines **4a–d**, **5a, b**

Method A: A mixture of dimethyl thioester (**3a** or **3b**; 0.01 mole) and primary diamine (0.03 mole), ethylene diamine, 1,2-propanediamine or 1,3-propanediamine was heated under reflux without solvent until evolution of methyl mercaptan almost completely ceased (methyl mercaptan detected by the yellow colour appears at lead acetate paper). Reaction time were about 8–10 h. The excess diamine was evaporated under reduced pressure and the resultant solid was recrystallized from the proper solvent to give the corresponding azines **4a–d** and **5a, b**; yield 70–75% (Table I).

Method B: A mixture of dithioester **2a** or **2b** and excess of diamine was fused until methyl mercaptan and hydrogen sulphide completely evaporated, the product separated as in method A; yield 53–58%.

Method C: A solution of (**2a** or **2b**; 0.01 mole) in absolute ethanol (50 ml) was refluxed with requisite diamine (0.01 mole) for 12 h. After cooling, the formed solid product is collected and recyrstallized

TABLE I

Physical data of dithioesters, azines and thiosemicarbazone derivatives

No of Compd.	m.p. °C	Solvent of cryst.	Yield %	Molecular Formula	Elemental Analysis Found/Calculated			
					%C	%H	%N	%S
2a	193	E	84	$C_{12}H_{17}N_3O_2S_3$	43.40	5.20	12.90	28.80
					43.50	5.14	12.69	29.00
2b	190	E	83	$C_{14}H_{21}N_3O_2S_3$	46.70	5.60	11.90	27.00
					46.80	5.85	11.70	26.74
3a	143	M	81	$C_{13}H_{19}N_3O_2S_3$	45.40	5.60	12.40	28.10
					45.22	5.51	12.17	27.83
3b	141	M	82	$C_{15}H_{23}N_3O_2S_3$	48.40	6.10	11.30	26.10
					48.26	6.17	11.26	25.74
4a	242	E	74	$C_{13}H_{19}N_5O_2S$	50.30	6.10	22.80	10.40
					50.49	6.15	22.65	10.36
4b	234	E	73	$C_{14}H_{21}N_5O_2S$	52.30	6.20	21.40	10.20
					52.01	6.50	21.67	9.91
4c	179	E	72	$C_{15}H_{23}N_5O_2S$	53.50	6.90	20.80	9.60
					53.41	6.82	20.77	9.50
4d	170	M	74	$C_{16}H_{25}N_5O_2S$	54.80	7.10	19.50	9.40
					54.70	7.12	19.94	9.17
5a	253	E	73	$C_{14}H_{21}N_5O_2S$	52.20	6.80	21.40	10.20
					52.01	6.50	21.67	9.91
5b	207	E	75	$C_{16}H_{25}N_5SO_2$	54.80	7.10	19.60	9.30
					54.70	7.12	19.94	9.12
6a	272	E–B	60	$C_{15}H_{22}N_4O_3S_2$	49.00	5.80	15.30	17.40
					48.65	5.95	15.14	17.30
6b	216	E	59	$C_{17}H_{26}N_4O_3S_2$	51.40	6.60	14.10	16.20
					51.20	6.53	14.07	16.08
7a	261	E–B	40	$C_{16}H_{24}N_4O_3S_2$	50.30	6.30	14.60	16.70
					50.00	6.25	14.58	16.67
7b	268	E–B	39	$C_{18}H_{28}N_4O_3S_2$	52.60	6.90	13.20	15.10
					52.43	6.80	13.59	15.53
8a	168	E	58	$C_{14}H_{22}N_4O_2S_2$	49.10	6.30	16.40	18.40
					49.12	6.43	16.37	18.71
8b	213	E–B	53	$C_{18}H_{22}N_4O_2S_2$	55.50	5.80	14.60	16.80
					55.38	5.64	14.36	16.41
8c	158	E	59	$C_{16}H_{26}N_4O_2S_2$	51.80	7.00	15.30	17.60
					51.89	7.02	15.14	17.30
8d	160	M	58	$C_{20}H_{26}N_4O_2S_2$	57.30	6.20	13.20	15.20
					57.42	6.22	13.40	15.31

B= Benzene E= Ethanol M= Methanol

from the proper solvent to give **4a–d** and **5a–b** mixed m.p. with samples obtained from methods A and B give no depression; yield 50–55%.

IR of **4** and **5**: ν 3300–3250 cm^{-1} (NH), ν 1600–1590 cm^{-1} (C=N). ^{1}HNMR of **4b** (DMSO-d_6): δ 1.3 (d, 3H; CH—$\underline{CH_3}$), δ 2.4 (s, 3H; CH_3—C=N), δ 2.7 (s, 6H; $N(CH_3)_2$), δ 3.2 (t, 2H; CH_2), δ 4.1 (m, 1H; CH), δ 7.2 (br, 1H; NH), δ 7.4 (br, 1H; NH), δ 8.0 (d, 2H: ArH_x), δ 8.4 (d, 2H: ArH_y). ^{1}HNMR of **5a** (DMSO-d_6): δ 1.9 (m, 2H; CH_2(b)), δ 2.4 (s, 3H; CH_3—C=N), δ 2.7 (s, 6H; $N(CH_3)_2$). δ 3.4 (m, 4H; CH_2(a)), δ 7.2 (br, 2H; —NH—C—NH), δ 8.2 (d, 2H; ArH_x), δ 8.4 (d, 2H; ArH_y). MS of **4b**: m/z 323 (M^+).

Preparation of Thiosemicarbazone Derivatives **6a, b** *and* **8a–d**

A solution of (**2a** or **2b**; 0.01 mole) in absolute ethanol (50 ml) was refluxed with morpholine, ethylamine or benzylamine (0.01 mole) until the evolution of methyl mercaptan almost completely ceased. The resultant thiosemicarbazones **6a, b** and **8a–d** recrystallized from the suitable solvent (Table I).

Reaction of Dithioesters **2a, b** *with Morpholine*:

A mixture of (**2a** or **2b**; 0.01 mole) and morpholine (0.02 mole) in *n*-butanol was refluxed until no more hydrogen sulphide gas evolved. The reaction mixture was concentrated and the product filtered, washed with light petroleum (bp. 60–80°) and recrystallized from the proper solvent to give **7a, b** (Table I).

IR of **6** and **8**: ν 3350–3200 cm^{-1} (NH), ν 1610–1600 cm^{-1} (C=N), ν 1260–1250 cm^{-1} (C=S). IR of **7**: ν 1610–1600 cm^{-1} (C=N).

^{1}HNMR of **6b** (DMSO-d_6): δ 1.2 (t, 6H; $N(CH_2\underline{CH_3})_2$), δ 2.3 (s, 3H; CH_3—C=N), δ 3.3 (5, 4H; CH_2NCH_2 morpholine), δ 3.5 (q, 4H, $N(\underline{CH_2}CH_3)_2$), δ 3.7 (t, 4H, CH_2OCH_2 morpholine), δ 8.2 (d, 2H; ArH_x), δ 8.4 (d, 2H; ArH_y), δ 9.1 (s, 1H; NH).

^{1}HNMR of **7a** (DMSO-d_6): δ 2.4 (s, 3H; CH_3—C=N), δ 2.6 (s, 3H; SCH_3), δ 2.8 (s, 6H; $N(CH_3)_2$), δ 3.3 (t, 4H; CH_2NCH_2 morpholine), δ 3.7 (t, 4H; CH_2OCH_2 morpholine), δ 8.2 (d, 2H; ArH_x), δ 8.4 (d, 2H; ArH_y).

^{1}HNMR of **8a** (DMSO-d_6): δ 1.1 (t, 3H; $CH_2CH_2\underline{CH_3}$), δ 1.8 (m, 2H; $CH_2\underline{CH_2}CH_3$), δ 2.4 (s, 3H; CH_3—C=N), δ 2.8 (s, 6H; $N(CH_3)_2$), δ 3.7 (m, 2H; N—$\underline{CH_2}CH_2CH_3$), δ 7.3 (br, 1H; NH), δ 8.2 (d, 2H; ArH_x), δ 8.4 (d, 2H; ArH_y), δ 9.1 (s, 1H; NH).

^{1}HNMR of **8d** ($CDCl_3$): δ 1.2 (t, 6H; $N(CH_2\underline{CH_3})_2$), δ 2.4 (s, 3H; CH_3—C=N), δ 3.4 (q, 4H; $N(\underline{CH_2}CH_3)_2$), δ 5.2 (d, 2H; N—CH_2), δ 7.2 (br, 1H; NH), δ 7.7–8.2 (9H; ArH), δ 9.2 (s, 1H; NH).

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