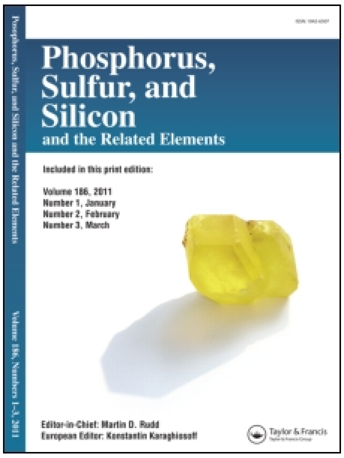

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REACTIONS WITH THIAZOLINONES: A NEW ROUTE FOR THE SYNTHESIS OF THIAZOLONYLPYRIDAZONE AND THIAZOLYLPYRAZOLONE DERIVATIVES

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REACTIONS WITH THIAZOLINONES: A NEW ROUTE FOR THE SYNTHESIS OF THIAZOLONYLPYRIDAZONE AND THIAZOLYLPYRAZOLONE DERIVATIVES

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2-Amino-1,1,3-tricyanoprop-1-ene (**1**) reacted with thioglycollic acid to afford the key compound for this study namely: 2-amino-1,1-dicyano-3(2-thiazolin-4-on-2-yl)prop-1-ene **2**. **2** reacted with hydrazines to afford the thiazolylmethylaminopyrazole derivatives **3** and **4**. The reaction of **2** with diazotised primary aromatic amines afforded coupling products which were cyclised to the hydrazothiazolonylpyridazine derivatives **7**. The reaction with aromatic aldehydes gave the bis-ylidene derivatives **8**. Structures are assigned based on elemental and spectroscopic analysis.

Key words: Thiazolones; thiazolonylpyridazones; thiazolylpyrazolones; thioglycollic acid; malononitrile dimer.

INTRODUCTION

The reported biological activities of thiazoles and thiazolones as tuberculostically active drugs,[1] antituberculous agents,[2] bacteriostatic activity agents[3] and fungistatic and mildew-preventing activity agents[4] together with their use as reagents in quantitative and qualitative analysis[5–7] besides their use as coloured photographic film developers[8–10] prompted the interest in the synthesis of derivatives of these ring systems. The reaction of malonitrile dimer **1** with thioglycollic acid seemed to be a logic and easy route for these syntheses.

RESULTS AND DISCUSSION

It has been found that 2-amino-1,1,3-tricyanoprop-1-ene (**1**, malononitrile dimer) reacted with thioglycollic acid (TGA) in glacial acetic acid to give a product corresponding to the addition of one molecule of **1** to one molecule of thioglycollic acid followed by the loss of one molecule of water. The reaction product has been assigned to the structure of 2-amino-1,1-dicyano-3(2-thiazolin-4-on-2-yl)-prop-1-

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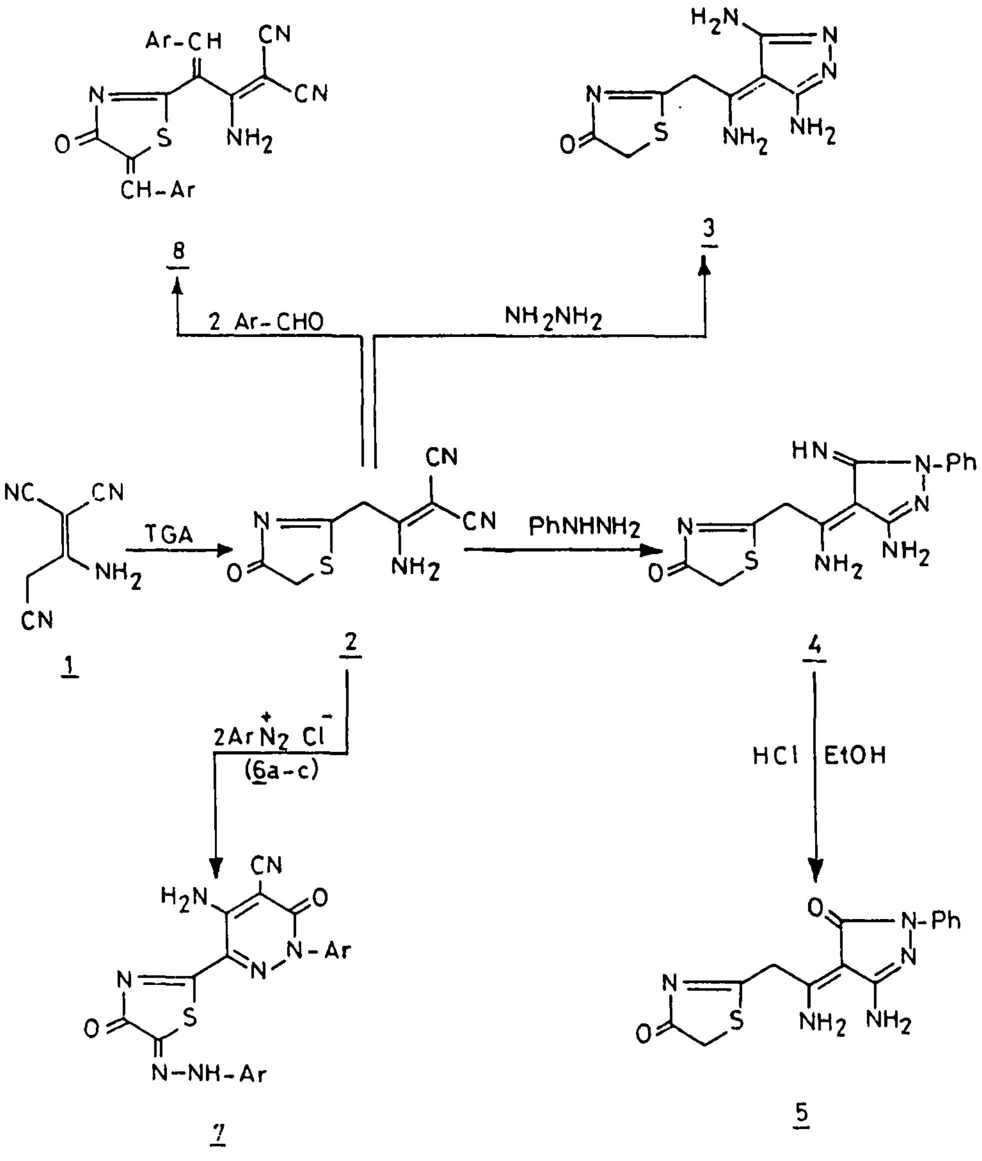
REACTIONS WITH DIMERIZED MALONONITRILE



6 - 8a, Ar = C_6H_5
b, Ar = C_6H_4-CH_3-p
c, Ar = C_6H_4-NO_2-p

ene **2** based on elemental analysis and spectral data. The IR spectrum of **2** showed peaks related to the presence of NH_2, saturated CH_2, two CN and ring CO groups. The ^{1}H-NMR spectrum of **2** revealed signals corresponding to the presence of NH_2, aliphatic CH_2 and thiazole-CH_2 groups. The synthetic potential of **2** as a polylfunctionalised synthon was demonstrated via its reactions with several reagents and consequently leading to several new heterocyclic derivatives required for both biological activity studies as well as for further chemical transformations. Thus, it has been found that **2** reacted with hydrazine hydrate in ethanol to afford thiazolylmethylaminomethylene diaminopyrazoline **3** based on elemental analysis and spectral data. The IR spectrum of **3** showed peaks related to the presence of NH_2, saturated CH_2 and ring CO groups and the bands attributible to the presence of the CN functions were entirely absent meaning that the two cyano groups in **2** were those which participated in the reaction with hydrazine hydrate leading to **3** (cf. Experimental Part). Similar to its behaviour towards hydrazine hydrate, compound **2** reacted also with phenylhydrazine to afford the pyrazoline derivative **4** whose structure was elucidated on the basis of elemental analysis and spectral data (cf. Experimental Part). A further proof of the structure of **4** was achieved via its conversion into the pyrazolin-5-one derivative **5** by boiling in ethanolic-hydrochloric acid. The structure of **5** was, in turn, elucidated based on elemental and spectral data studies (cf. Experimental Part).

The investigation was also extended to study the behaviour of **2** towards diazotised primary aromatic amines. Thus, it has been found that compound **2** coupled with the diazotised primary aromatic amines **6a–c** to afford products corresponding to the addition of two molecules of **6a–c** followed by hydrolysis. The reaction products can be formulated as the thiazolyl pyridazinone derivatives **7a–c** based on both elemental and spectral data. The IR spectra of **7a–c** showed absorption peaks related to the presence of NH_2, NH, CN and ring CO groups. The ^1H-NMR spectra of **7a–c** revealed a pattern which could only be intelligibly interpreted in terms of structure **7a–c**. It is remarkable to note here that the monoazo-coupling

TABLE I

Characterisation data of the newly synthesised derivatives

Comp.	M.P. (°C)	Cryst. Solv.	Yield (%)	Mol. Formula	% Analysis C	H	Calcd. Found N	S
2	>300	DMF/H_2O	75	$C_8H_6N_4OS$	46.59	2.92	27.16	15.54
					46.60	2.90	27.20	15.55
3	275	Acetic acid	70	$C_8H_{10}N_6OS$	40.32	4.23	35.27	13.45
					40.35	4.25	35.20	13.55
4	295	Acetic acid	70	$C_{14}H_{14}N_6OS$	53.48	4.48	26.73	10.19
					53.44	4.50	26.69	10.20
5	>300	Ethanol	80	$C_{14}H_{13}N_5O_2S$	53.32	4.15	22.20	10.16
					53.35	4.18	22.25	10.11
7a	212	Acetic acid	75	$C_{20}H_{13}N_7O_2S$	57.82	3.15	23.59	7.71
					57.77	3.15	23.55	7.73
7b	225–6	Acetic acid	75	$C_{22}H_{17}N_7O_2S$	59.58	3.86	22.10	7.22
					59.55	3.84	22.20	7.17
7c	245–7	Acetic acid	75	$C_{20}H_{11}N_9O_6S$	47.52	2.19	24.94	6.34
					47.50	2.13	24.90	6.40
8a	248–9	DMF/H_2O	85	$C_{22}H_{14}N_4OS$	69.09	3.68	14.64	8.38
					69.11	3.66	14.58	8.34
8b	262–3	DMF/H_2O	85	$C_{24}H_{18}N_4OS$	70.22	4.41	13.64	7.81
					70.20	4.41	13.63	7.80
8c	268–9	DMF/H_2O	85	$C_{22}H_{12}N_6O_5S$	55.93	2.55	17.78	6.78
					55.90	2.57	17.78	6.77

products could not be obtained under the applied reaction conditions and the reactants reacted in a molar ratio of 1:2 in each case.

On the other hand, **2** reacted with aromatic aldehydes to afford the bis-ylidene derivatives **8a–c**. The structure of **8a–c** was established on the basis of elemental analyses and spectral data studies (cf. Experimental Part). Again it is remarkable to note that all trials to synthesise the mono-ylidene derivatives were unsuccessful and the bis-ylidenes were the only isolable reaction products even on using the reactants in a molar ratio of 1:1.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 spectrophotometer using KBr discs. ^1H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer using DMSO-d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. The microanalyses were performed by the microanalytical center at Cairo University.

Reaction of **1** *with thioglycollic acid.* A solution of **1** (0.01 mol) and thioglycollic acid (0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 3 hours. The solvent was removed under reduced pressure and the solid product so formed was crystallised from the proper solvent to afford **2** (cf. Tables I and II).

TABLE II

IR and ^1H NMR spectral data

Comp.	IR (cm^{-1})	^1H NMR (δ ppm)
2	3450, 3380, 3290 (NH_2 group); 2250, 2160 (CN group) and 1720 (CO).	2.2 (s, 2H, CH_2); 3.2 (s, 2H, CH_2) and 5.6 (s, br. 2H, NH_2).
3	3450, 3380, 3280, 3170 (NH_2 groups) and 1710 (CO).	2.2 (s, 2H, CH_2); 3.2 (s, 2H, CH_2) and 6.2–6.4 (s, br., 6H, 3 NH_2).
4	3450, 3390, 3300, 3280 (NH and NH_2 groups) and 1715 (CO).	2.2 (s, 2H, CH_2); 3.3 (s, 2H, CH_2); 6.3 (s, br, 4H, 2NH_2); 7.1–7.5 (m, 5H, ArH's) and 9.1 (s, br, 1H, NH).
5	3440, 3380, 3290 (NH_2 group) and 1720, 1700 (CO group).	2.2 (s, 2H, CH_2); 3.3 (s, 2H, CH_2); 6.2 (s, br, 4H, 2 NH_2); and 7.1–7.3 (m, 5H, ArH's).
7a	3350, 3270, 3180 (NH and NH_2 group); 2220 (CN) and 1710, 1690 (CO group).	5.6 (s, br, 2H, NH_2) and 7.1–8.2 (m, 11 H, ArH's and NH).
7b	3350, 3270, 3180 (NH and NH_2 group); 2220 (CN) and 1710, 1690 (CO group).	2.3 (s, 6H, 2 $ArCH_3$-p); 5.6 (s, br, 2H, NH_2) and 7.1–8.2 (m, 9H, ArH's and NH).
7c	3350, 3270, 3180 (NH and NH_2 group); 2220 (CN) and 1710, 1690 (CO group).	5.6 (s, br, 2H, NH_2) and 7.1–8.2 (m, 9H, ArH's and NH).
8a	3350, 3280 (NH_2); 2260, 2200 (CN groups) and 1690 (CO).	5.6 (s, br, 2H, NH_2); 6.9 (s, 1H, CH); 7.0 (s, 1H, CH) and 7.2–7.5 (m, 10 H, ArH's).
8b	3350, 3280 (NH_2); 2260, 2200 (CN groups) and 1690 (CO).	2.3 (s, 6H, 2 $ArCH_3$-p); 5.6 (s, br, 2H, NH_2); 6.9 (s, 1H, CH); 7.0 (s, 1H, CH) and 7.2–7.5 (m, 8H, ArH's).
8c	3350, 3280 (NH_2), 2260, 2200 (CN groups) and 1690 (CO).	5.6 (s, br, 2H, NH_2); 6.9 (s, 1H, CH); 7.0 (s, 1H, CH) and 7.2–7.5 (m, 8H, ArH's).

Reactions of **2** *with hydrazines.* A solution of **2** (0.01 mol) and each of hydrazinehydrate or phenylhydrazine (0.01 mol) in absolute ethanol was heated under reflux for 2 h and then the solvent was evaporated in vacuo. The solid product thus obtained was then filtered off and crystallised from the proper solvent to give **3** and **4** respectively (cf. Tables I and II).

Conversion of **4** *into* **5**. A solution of **4** (1 g) in ethanol (30 ml) was treated with conc. HCl (3 ml) and the whole was heated under reflux for 3 h. The solvent was removed in vacuo, and the product so formed was filtered off, washed with water and then crystallised from the proper solvent to give **5** (cf. Tables I and II).

Coupling of **2** *with* **6a–c**. A cold solution of **2** (0.01 mol) in ethanol (30 ml) and sodium acetate (2 g) was added dropwise to cold stirred solution of the appropriate diazotised primary aromatic amines (**6a–c**; 0.022 mol). The reaction mixture was then allowed to stand in the ice chest for 5 h. The solid product so formed was collected by filtration, washed with water and then crystallised from the proper solvent to give **7a–c** (cf. Tables I and II).

Reactions of **2** *with aromatic aldehydes.* A solution of **2** (0.01 mol) and the appropriate aromatic aldehyde (0.022 mol) in ethanol (30 ml) and triethylamine (1 ml) was heated under reflux for 5 h. The solvent was removed and the product so formed was collected by filtration and crystallised from the proper solvent to give **8a–c** (cf. Tables I and II).

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