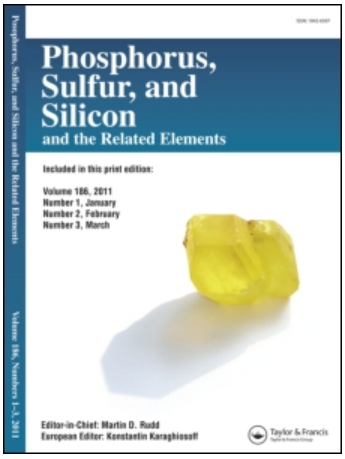

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Ring Opening-Ring Closure of 4-Phenyl-1,2-dithiole-3-thione: Reaction with α,β-Unsaturated Nitriles

Magda A. Barsy[a]
[a] South Valley University, Aswan, Egypt

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RING OPENING-RING CLOSURE OF 4-PHENYL-1,2-DITHIOLE-3-THIONE: REACTION WITH α,β-UNSATURATED NITRILES

Magda A. Barsy
South Valley University, Aswan, Egypt

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*4-Phenyl-1,2-dithiole-3-thione (**1**) reacts with unsaturated nitriles including β-arylacrylo-nitrile and crotonitrile derivatives. Thiinthione (**8**) was the only product obtained in all cases, which resulted from initial nucleophilic attack at C-5 of the dithiole ring. On the other hand compound (**1**) reacted with bromine followed by some selected amino-α, β-unsaturated nitriles to afford isothiazolo[3,2-b]-[1,3]thiazine derivatives mainly from nucleophilic attack at either C-3 or ring sulfur atom.*

Keywords: 4-Phenyl-1,2-dithiole-3-thione; α,β-unsaturated nitrile; isothiazolo[3,2][1,3]thiazine; thiinthione

Although different reactions of 1,2-dithiole-3-thiones with various reagents have been studied widely,[1–5] much less has been reported on these reactions toward unsaturated nitriles. In previous work we have reported on the reaction of (**1**) with some selected α,β-unsaturated nitriles incorporating active methylene groups,[6] here we wish to extend our investigations on the reactivity of (**1**) toward further selected α, β-unsaturated nitriles including acrylonitrile and crotonitrile derivatives. This also is done in connection with our interest in the synthesis[7–11] of new heterocycles needed for biological activity. Thus 4-phenyl-1,2-dithiole-3-thione (**1**) was allowed to react with compounds (**2a–c**) (where R=H) in refluxing ethanol in presence of piperidine as a catalyst to yield thiinthione (**8**) as the sole and only product in all cases. The structure of the products was established based on elemental analysis and spectral data. According to their mass spectra, the molecular weights were

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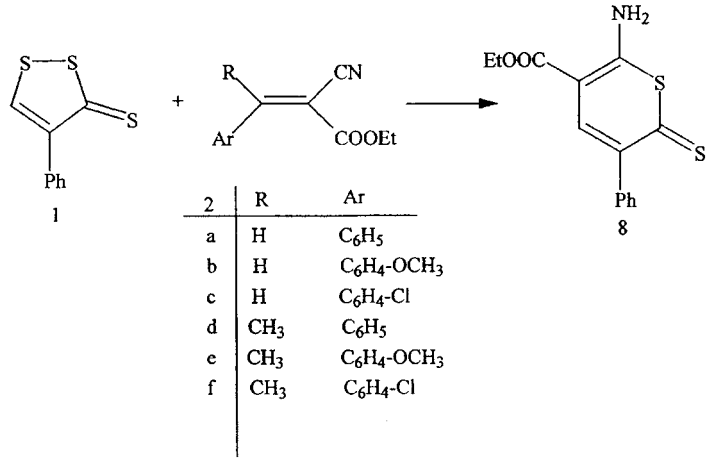
Address correspondence to Magda A. Barsy, Department of Chemistry, Faculty of Science, South Valley University, Aswan 81528, Egypt. E-mail: magdabarsy@hotmail.com



2	R	Ar
a	H	C_6H_5
b	H	C_6H_4-OCH_3
c	H	C_6H_4-Cl
d	CH_3	C_6H_5
e	CH_3	C_6H_4-OCH_3
f	CH_3	C_6H_4-Cl

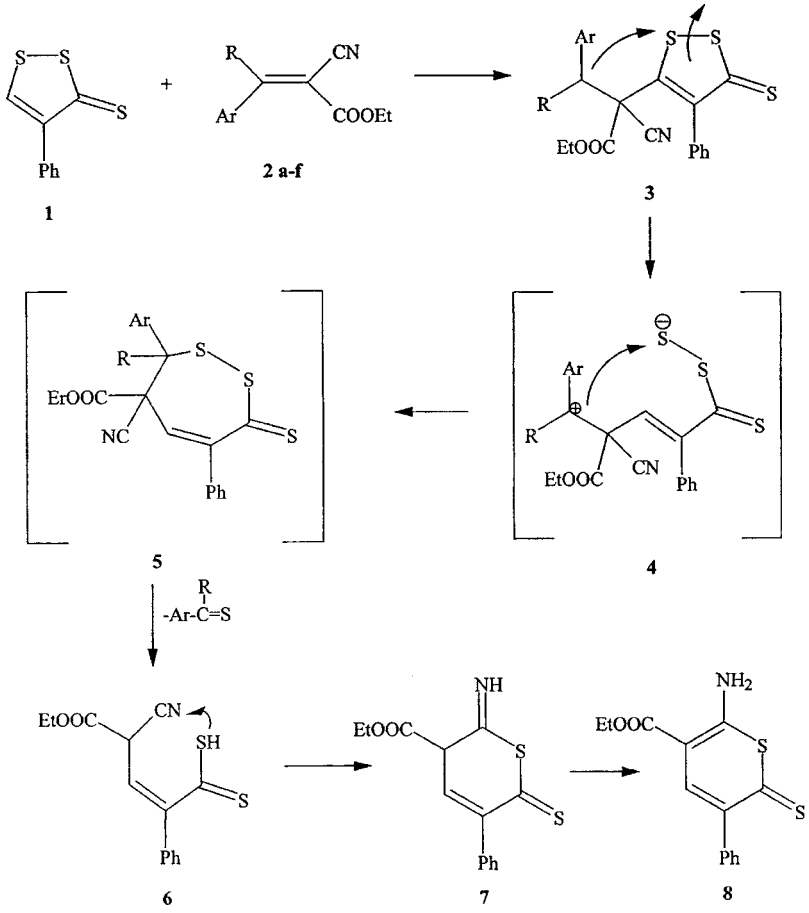
measured and found to be 291 [m/z at 291 (M^+)], the IR spectra resembled each others; the obsorption band assigned to cyano group was absent and instead showed absorption bands at $\nu = 3350–3200$ cm^{-1}, this fact indicated that the cyano group participated in the reaction. ^1H NMR spectra were in accordance with the assigned structure (**8**).

It is difficult to explain the formation of (**8**) on the basis of initial attack at C-3 or at ring sulfur, but simple in terms of initial attack at C-5, thus a nucleophilic attack at C-5 would lead to ring opening to afford acyclic thione (**4**), which recyclises to a 7 membered ring intermediate (**5**) (many examples have been observed before),[12] this undergoes thiobenzaldehyde extrusion affording (**6**). Addition-cylization of (**6**) would give the final thiinthione (**8**).

Retention of the thione group in the final cyclic product (**8**) indicates that the C-3 is not the site of initial attack. On the other hand attack on ring sulfur would lead to the formation of the γ-thiinthione tautomer (c.f. Scheme 1).

Similarly, compound (**1**) reacted with crotonitrile derivatives (**2d–f**) (where R=CH_3), to afford (**8**) through similar reaction mechanism.

On the other hand treatment of 4-pheny-1,2-dithiole-3-thion with bromine, followed by 2-amino-1,1,3-tricyanopropene (**10a**) and/or its derivative (**10b**) in ethanol at room temperature afforded the corresponding isothiazolo[3,2-b][1,3]thiazines (**13a**) and (**13b**), respectively, in good yields. The establishment of the structure of products (**13a,b**) depends (apart from elemental analysis) on the mass spectrum, which indicated m/z at 309 (M-1) for (**13a**), on strong IR absorption bands at 3416–3303; 2222, 2204, and finally on its ^1H NMR spectrum which exhibited in addition to the aromatic proton region (7.2–7.9)) two signlet



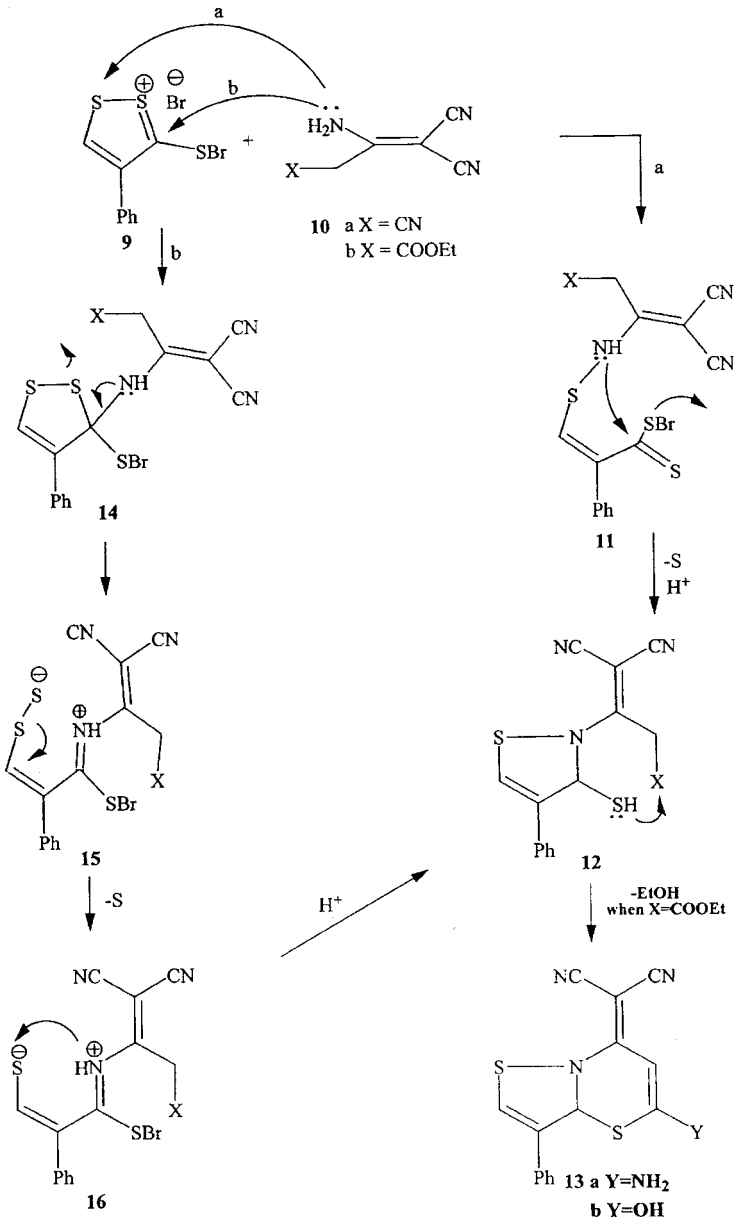
SCHEME 1

signals due to one proton at $\delta = 2.9$ ppm and at $\delta = 6.2$ ppm for the NH_2 group. Whereas (**13b**) showed m/z (M-1) at 310.

Formation of (**13a**) and (**13b**) could be rationalized by nucleophilic attack on either the ring sulfur (path a), or carbon 3 (path b) at the initially formed 3-bromothiodithiolium bromide (**9**). These are corresponding to previously reported mechanisms.[13,14]

A concomitant nitrogen nucleophilic attack at the ring sulfur followed by intramolecular lone pair attack on C-3 would give the isothiazoline derivative intermediates (**12**), which cyclized to the final bicyclic product (**13**) after losing sulfur and protonation. (c.f. Scheme 2).

Formation of (**13**) also must arise through preferential attack of the initial nitrogen nucleophiles (**10a,b**) at C-3 to give intermediate (**14**)



SCHEME 2

which undergoes ring opening, and then extrude sulfur. Recyclization and protonation would give the same intermediate (**12**) as in path a, this undergoes the same cyclization sequence to the final products (c.f. Scheme 2, path b). Had the nucleophilic attack took place on carbon 5, N-substituted isothiazoline-5-thione would have been expected.[15]

These results are in accordance with our previous findings on the nucleophilic attack of nitrogen nucleophiles on isothiazolium salts.[16]

EXPERIMENTAL

Melting points reported are uncorrected. The IR spectra (KBr wafer, $\nu = cm^{-1}$) were recorded on a Shimadzu 408 and a Pye Unicam Spectrophotometer. The ^1H NMR spectra were recorded on a Varian EM-390-90 MHz Spectrometer with DMSO-d6 as a solvent and TMS as internal reference. The chemical shifts are expressed in ppm.

6-Amino-5-ethoxycarbonyl-3-phenyl Thiinthione (8)

To a mixture of 4-phenyl-1,2-dithiol-3-thione[17] (**1**) (2.1 g, 0.01 mmol) and the appropriate nitrile (**2a–b**) (0.01 mmol) in 30 ml ethanol an 0.5 ml of piperidine was added. The mixture was refluxed for 5 h (monitored by TLC). The solvent was evaporated in vacuo, the solid product so formed was collected by filtration and recrystallized from dioxane to give orange needle's in 83% yield (2.4 g). m.p. 240°C. IR (KBr, $\nu = cm^{-1}$): 3350–3200 (NH_2), 1695, 1620 (C=O), 1150, (C=S). ^1H NMR (DMSO, δ = ppm): 1.2 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 6.3 (br, 2H, NH_2), 7.2–8.1 (m, 6H, Ar—H and thiin-γ-proton). MS, m/z = 293 (M + 2, 10%), 292 (M + 1, 19%), 291 (M_+, 100%), 243 (19%), 216 (27%), 201 (13%), 145 (34%), 190 (15%). Calcd. for $C_{14}H_{13}NO_2S_2$ (291): C 57.70, H 4.49, N 4.80, S 22.00; Found: C 57.53, H 4.54, N 4.73, S 22.11.

Reaction of 4-Phenyl-1,2-dithiole-3-thione with 10a and 10b

General Procedure

4-Phenyl-1,2-dithiole-3-thione (**1**) (2.10 g, 0.01 mmol) dissolved in carbon tetrachloride (50 ml) was treated slowly with a solution of bromine (1.76 g, 0.011 mmol) in carbon tetra chloride (20 ml) by stirring. The tan solid formed was collected, washed with carbon tetrachloride, and briefly dried to remove excess carbon tetrachloride. The solid was added portionwise to solutions of desired aminonitrile **10a** or **10b** (0.05 mmol) in ethanol 50 ml by stirring; a reaction induced. After

20 min, the mixture was diluted with water and the product stirred with 10% hydrochloric acid. The mixture was left overnight and the solid product so formed was collected by filtration and crystallized from ethanol.

2-Amino-4-dicyanomethylene-7-phenyl-isothiazolo-[3,2-b][1,3]thiazine (13a)

Yellow crystals 72% yield. m.p. 310°C. IR (KBr, $\nu = cm^{-1}$): 3416, 3303 (NH_2), 2222, 2204, (CN), 1644 (C=C). ^1H NMR (DMSO, δ = ppm): 2.9 (s, 1H) 6.2 (br, 2H, NH_2), 7.2–7.9 (m, 5H, Ar—H). MS, m/z = 309 (M-1, 87%), 253 (13%), 215 (11%), 183 (11%), 140 (12%), 92 (43%), 86 (100%), Calcd. for $C_{15}H_{10}N_4S_2$ (310.38): C 58.04, H 3.25, N 18.05, S 20.66; Found: C 58.53, H 3.54, N 17.89, S 20.11.

2-Hydroxy-4-dicyanomethylene-7-phenyl-isothiazolo-[3,2-b][1,3]thiazine (13b)

Yellow crystals, 67% yield. m.p. 170°C. IR (KBr, $\nu = cm^{-1}$): (OH), 2226, 2198 (CN), 1630 (C=C). ^1H NMR (DMSO, δ = ppm): 2.8 (s, 1H), 7.2–8.1 (m, 5H, Ar—H). MS, m/z = 310 (M-1, 15%), 309 (100%), 253 (33%), 226 (13%), 140 (17%), 92 (62%), 66 (34%), Calcd. for $C_{15}H_9N_3S_2O$ (311.37): C 57.85, H 2.91, N 13.49, S 20.59; Found: C 57.63, H 2.89, N 13.60, S 20.31.

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