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Ring opening-ring closure of 4-phenyl-1,2-dithiole-3-thione: convenient route to novel thiinethione derivatives by the reaction with active methylene nitriles

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Ring opening–ring closure of 4-phenyl-1,2-dithiole-3-thione: convenient route to novel thiinethione derivatives by the reaction with active methylene nitriles

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4-Phenyl-1,2-dithiole-3-thione (**1**) reacts with active methylene nitriles in the presence of triethylamine to afford fused and isolated thiine derivatives, mainly from initial nucleophilic attack of methylene group at C-5 of the dithiole ring.

Keywords: 4-phenyl-1,2-dithiole-3-thione; 2-amino-1,1-dicyano-3-ethoxycarbonyl-1-propene; 2-cyanomethylbenzimidazole; thiino[2,3-b]pyran-2-thione; thiinethione

1. Introduction

The reactivity of 1,2-dithiole-3-thiones has been extensively investigated (*1–11*). Its utility as a precursor of new sulfur compounds was reported (*12–16*), while the mechanistic pathway of its reactions has received additional concern (*17–20*). In the previous work, we reported that the reaction of 4-phenyl-1,2-dithiol-3-thione (**1**) with some selected α, β-unsaturated nitriles does in fact take place on the C-5 of the dithiole ring as the preferential site of nucleophilic attack (*21*, *22*); here, we wish to report our investigations on the reactivity of (**1**) toward active methylene nitriles.

2. Results and discussion

The reaction of (**1**) with 2-amino-1,1-dicyano-3-ethoxycarbonyl-1-propene (**2a**, X = CN) in refluxing ethanol in the presence of triethylamine as a catalyst afforded thiino[2,3-b]pyrane (**6**) in a good yield. The structure of (**6**) was established based on its spectral and analytical data. Its mass spectrum indicated molecular ion at m/z 311 (M^+). The IR showed absorption bands at ν 3350, 3110 and 2218 cm^{-1} corresponding to the spectra of amino, imino and cyano groups, respectively. The ^{1}H-NMR spectrum of the product revealed the presence of a singlet at $\delta = 6.2$ ppm for NH_2,

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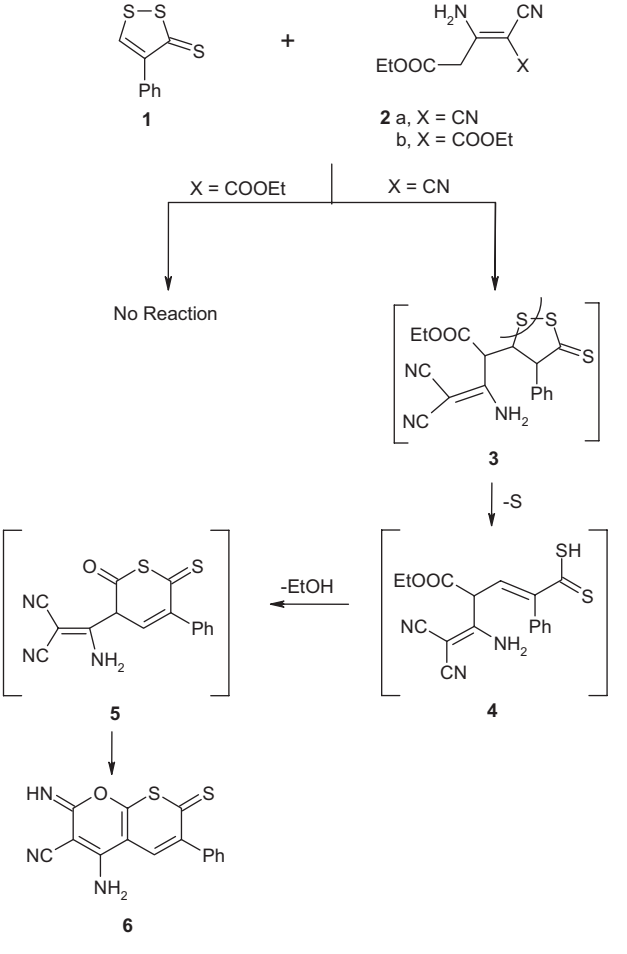
a multiplet at $\delta = 7.1$–7.9 ppm for aromatic protons and a singlet at $\delta = 12.1$ for NH. As detailed in Section 3, ^{13}C-NMR spectra showed all expected signals of compound (**6**), but did not include the signals due to the ethoxy group, such data agree with the structure (**6**). It is difficult to explain the formation of (**6**) on the basis of initial nucleophilic attack at C-3 or at ring sulfur, but readily in terms of initial attack at C-5, as this position has been reported to readily undergo nucleophilic attack (*23*). The most likely scheme for the formation of (**6**) would involve deprotonation by base to form the Michael adduct (**3**) which looses a sulfur atom probably from a –S-SH group (*23*, *24*) released during the ring opening of (**3**) to generate (**4**) which could be subsequently recyclized to (**5**) via ethanol elimination, followed by a heterocyclization to afford the final product (**6**). Neither prolonged treatment of (**1**) with (**2b**, X = COOEt) under the same reaction condition nor fusion at 150 °C resulted in a product possibly because of steric hindrance (Scheme 1).

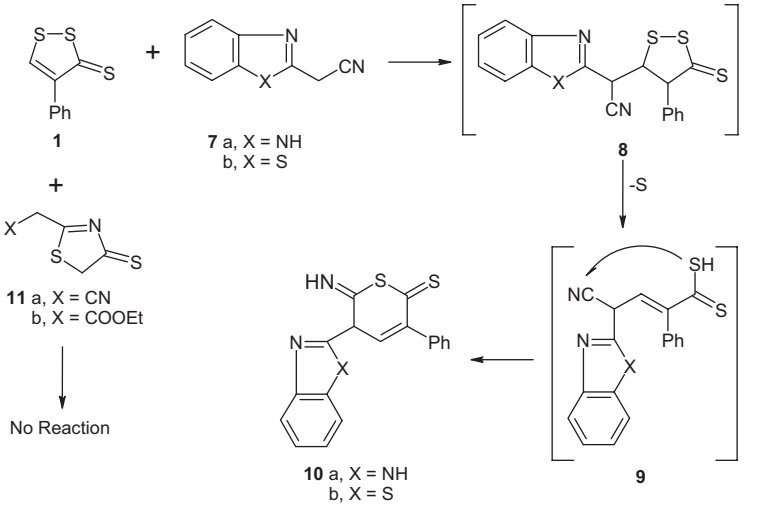


Scheme 1. Reaction conditions, EtOH, TEA, reflux, 3 h or heating above the melting point.

When compound (**1**) reacted with 2-cyanomethylbenzimidazole (**7a**, X = NH) in refluxing ethanol in the presence of catalytic amounts of triethylamine, the thiinethione derivative (**10a**, X = NH) was obtained, suggesting that the position of initial nucleophilic attack is also at C-5 of the dithiole ring, the reaction proceeds through intermediate (**8**). Under basic conditions, the S–S bond is ruptured, leading to ring opening, followed by loss of one sulfur atom, as discussed

before, to give intermediate (**9**), which subsequently cyclized via the nucleophilic addition of thiol sulfur onto the carbonitrile carbon to yield eventually the thiinethione derivative (**10a**). Likewise compound (**1**) reacted with 2-cyanomethylbenzothiazole (**7b**, X = S) to give the thiinethione derivative (**10b**, X = S). Structure of **10a** and **10b** was established based on spectral and elemental data. The IR spectra showed no absorption bands due to nitrile function, whereas sharp bands were recorded at 3110 and 3120 cm^{-1} assigned to NH function.

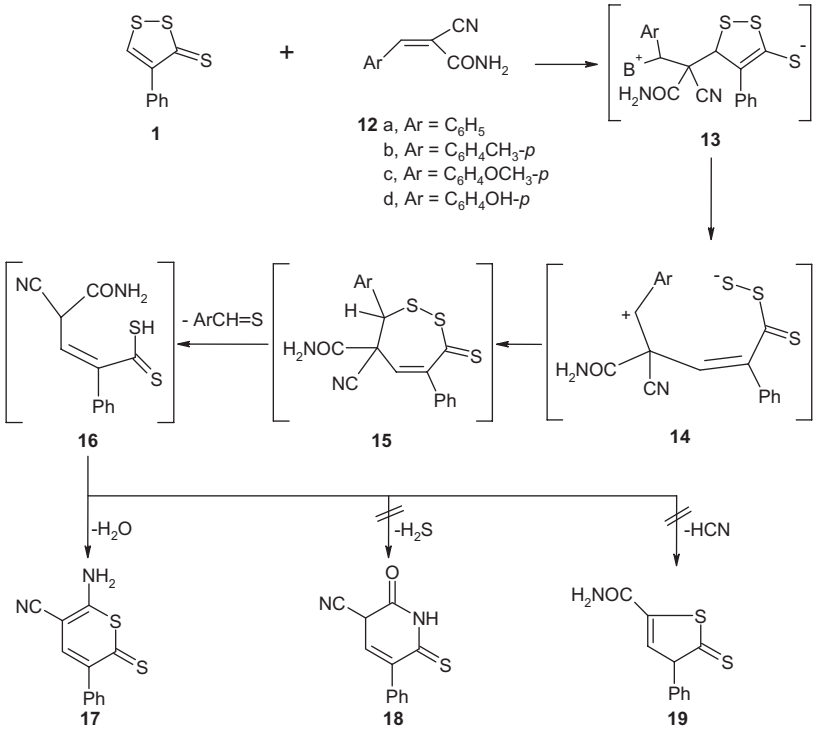
Treatment of (**1**) with 2-cyanomethy-1,3-thiazolidine-4-thione (**11a**) and 2-ethoxycarbonyl-1,3-thiazolidine-4-thione (**11b**) under the same reaction condition resulted in decomposition. It seems that in the case of the former reaction, intermediates (**8**,**9**) are stabilized by the aromatic ring (Scheme 2).



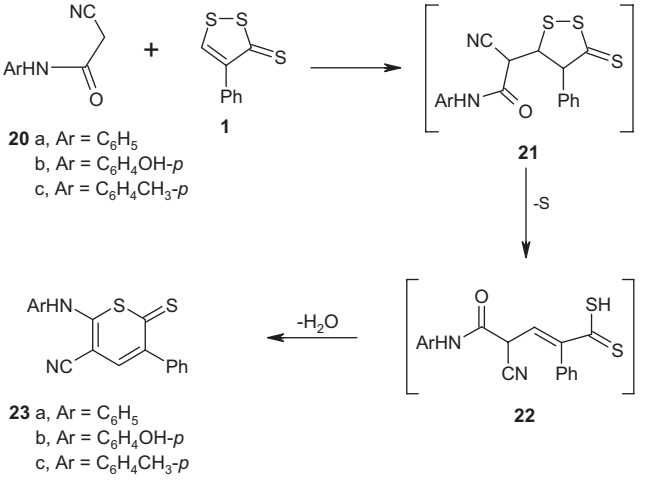
Scheme 2. Reaction conditions, EtOH, TEA, reflux, 4–6 h.

On the other hand, when compound (**1**) was heated at 150 °C with arylidenecyanoacetamide derivatives (**12a**–**12d**) in a heating mantle in the presence of a few drops of triethylamine, the corresponding thiinethione derivative (**17**) was formed as the sole and only product in all cases. The melting points, the mass spectra and the IR spectra of the resulting products resemble each other. The mass spectra revealed M^+ at m/z 244. In the IR spectra, the absorption band assigned to cyano group was present. These facts indicate that the cyano group does not participate in the reaction. Unexpectedly, structure (**17**) was suggested for reaction product rather than structures (**18**) and (**19**), which could be produced by losing hydrogen sulfide or hydrogen cyanide, respectively. These data could explain the formation of (**17**) via initial nucleophilic attack on C-5; this would lead to ring opening to give acyclic thione (**14**) which recyclized to a seven-membered ring intermediate (*25*) (**15**) which is not stable and undergoes thiobenzaldehyde extrusion affording intermediate (**16**). Recyclization via loss of water molecule would give the final product (**17**) (Scheme 3).

As an extension of this reaction, compound (**1**) was allowed to react with *N*-arylcyanoacetamide derivatives (**20a**–**20c**), the thiine derivatives (**23a**–**23c**) were provided. Structures of (**23a**–**23c**) were established based on both spectral and elemental data. The mass spectrum of compound (**23a**, Ar = Ph) indicated m/z at 320 (M^+), and IR showed absorption bands at 3130 and 2223 cm^{-1}. ^{1}H-NMR was identical with the structure of compound (**23a**). It appears that in this case also ring cleavage is the dominant reaction, possibly by initial nucleophilic attack at C-5 of the thiole ring. Cyclization occurs by loss of water molecule rather than hydrogen sulfide with the formation of (**23**). These results are comparable to other such studies made by us (*21*, *22*) (Scheme 4).



Scheme 3. Reaction conditions, heating at 150 °C in heating mantel, TEA, 1 h.



Scheme 4. Reaction conditions, EtOH, TEA, reflux, 5 h.

3. Experimental

Melting points were determined on a Gallenkamp electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide pellets using an FTIR unit

Bruker-vector 22 Spectrophotometer; ^{1}H-NMR and ^{13}C-NMR spectra were obtained in deuterated dimethyl sulfoxide as a solvent at 300 MHz and 75 MHz, respectively, on a Varian Gemini spectrometer using TMS as the internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were recorded on a Hewlett Packard MS-5988 spectrometer at 70 eV. Elemental analysis was carried out at the Micro Analytical Center of Cairo University, Egypt.

3.1. *5-Amino-6-cyano-7-imino-3-phenylthiino[2,3-b]pyran-2-thione (6)*

To a mixture of 4-phenyl-1,2-dithiol-3-thione (*26*, *27*) (**1**) (2.1 g, 0.01 mmol) and 2-amino-1,1-dicyano-3-ethoxycarbonyl-1-propene (**2a**, X = CN) (1.6 g, 0.01 mmol) in ethanol (30 ml), 0.5 ml of triethylamine was added. The reaction mixture was refluxed for 3 h. The solvent was removed *in vacuo*; the solid product so formed was collected by filtration and crystallized from (EtOH/dioxane 3:1) as dark red needles.

Yield: (260 mg), 83%, m.p.: >300 °C. IR: (KBr, ν = cm^{-1}) 3350–3320 (NH_2), 3110 (NH), 2218 (CN), 1154 (C=S); ^{1}H-NMR: (DMSO, δ = ppm) 6.23 (s, 2H, NH_2), 7.12–7.90 (m, 6H, Ar-H and thiine γ-proton), 12.14 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, TMS): δ 118.22, 122.27, 127.77, 128.20, 129.11, 129.91, 132.62, 134.33, 135.08, 139.37, 141.88, 143.10, 153.12, 160.65, 205.77; MS m/z = 311 (M^+, 69%), 309 (M-2, 100%), 266 (31%), 66 (24%). Calcd. for $C_{15}H_9N_3OS_2$ (311.38): C, 57.86; H, 2.91; N, 13.50; S, 20.59; found: C, 57.81; H, 2.86; N, 13.47; S, 20.56.

3.2. *5-(Benzyimidazol-2-yl)-6-imino-3-phenyl-thiine-2-thione (10a)*

A mixture of (**1**) and 2-cyanomethylbenzimidazole (**7a**, X = NH) (1.6 g, 0.01 mmol) in 30 ml of ethanol containing catalytic amounts of triethylamine was refluxed for 4–6 h. The solid product so formed was collected by filtration and crystallized from EtOH/H_2O (3:1) as buff powder.

Yield: (251 mg), 75%, m.p.: 260–261 °C. IR: (KBr, ν = cm^{-1}) 3110 (NH), 1155 (C=S); ^{1}H-NMR: (DMSO, δ = ppm) 6.21 (d, 1H, thiine-H, J = 3.9 Hz), 7.00 (d, 1H, thiine-H, J = 3.8 Hz), 7.33–7.95 (m, 9H, Ar-H), 8.91 (s, 1H, NH), 12.77 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, TMS): δ 118.87, 119.00, 128.16, 128.67, 128.98, 129.15, 129.98, 130.09, 131.14, 132.21, 133.86, 134.18, 134.32, 135.73, 142.00, 149.27, 207.78; MS m/z = 334 (M-1, 100%), 300 (50%), 275 (13%), 257 (11%), 151 (10%), 102 (20%), 77 (10%), 65 (29%). Calcd. for $C_{18}H_{13}N_3S_2$ (335.44): C, 64.45; H, 3.91; N, 12.53; S, 19.12; found: C, 64.41; H, 3.88; N, 12.50; S, 19.09.

3.3. *5-(Benzythiazol-2-yl)-6-imino-3-phenyl-thiine-2-thione (10b)*

The reaction was performed as previously described except that 2-cyanomethylbenzthiazole (**7b**, X = S) was used, crystallized from EtOH/H_2O (3:1) as red crystals.

Yield: (253 mg), 72%, m.p.: 250–251 °C. IR: (KBr, ν = cm^{-1}) 3120 (NH), 1150 (C=S); ^{1}H-NMR: (DMSO, δ = ppm) 6.09 (d, 1H, thiine-H, J = 3.4 Hz), 7.02 (d, 1H, thiine-H, J = 3.6 Hz), 7.31–7.98 (m, 9H, Ar-H), 12.79 (s, 1H, NH). MS m/z = 352 (M^+, 100%), 337 (55%), 305 (23%), 275 (12%), 257 (12%), 151 (13%), 102 (25%), 77 (12%), 65 (26%). Calcd. for $C_{18}H_{12}N_2S_3$ (352.49): C, 61.33; H, 3.43; N, 7.95; S, 27.29; found: C, 61.30; H, 3.39; N, 7.91; S, 27.26.

3.4. *Reaction of 4-phenyl-1,2-dithiole-3-thione (1) with arylidenecyanoacetamide (12a–12d)*

A mixture of an equimolar amount of (**1**) (0.01 mmol) and appropriate arylidenecyanoacetamide (**12a**–**12d**) was heated at 150 °C in heating mantel in the presence of a catalytic amount of triethylamine (three to five drops) for 1 h. The resulting product was treated with ethanol. The solvent was removed and a brown solid was obtained in all cases.

3.5. *6-Amino-5-cyano-3-phenyl-thiine-2-thione (17)*

Crystallized from ethanol. Yield: 62–58%, m.p.: >300 °C. IR: (KBr, $\nu = \text{cm}^{-1}$) 3370 (NH_2), 2220 (CN), 1145 (C=S); ^{1}H-NMR: (DMSO, $\delta =$ ppm) 4.66 (s, 2H, NH_2), 7.10–7.81 (m, 6H, Ar-H, and thiine γ-proton); ^{13}C-NMR (DMSO-d_6, TMS): δ 118.22 122.54, 127.89, 128.11, 128.60, 129.77, 132.66, 134.21, 135.71, 139.34, 141.81, 142.66, 205.32; MS $m/z = 244$ (M^+, 17%), 236 (38%), 219 (20%), 194 (23%), 154 (20%), 127 (27%), 82 (11%), 56 (24%). Calcd. for $C_{12}H_8N_2S_2$ (244.33): C, 58.99; H, 3.30; N, 11.47; S, 26.24; found: C, 58.96; H, 3.26; N, 11.42; S, 26.20.

3.6. *Reaction of 4-phenyl-1,2-dithiol-3-thione (1) with N-arylcyanoacetamide (20a–20c)*

3.6.1. *General procedure*

To a mixture of 4-phenyl-1,2-dithiol-3-thione (**1**) (2.1 g, 0.01 mmol) and appropriate *N*-arylcyanoacetamide (0.01 mmol) in ethanol (30 ml), 0.5 ml of triethylamine was added. The reaction mixture was refluxed for 5 h. The solvent was removed *in vacuo*; the solid product so formed was collected by filtration and crystallized from a proper solvent.

3.7. *5-Cyano-3-phenyl-6-(phenylamino)thiine-2-thione (23a)*

Buff powder from ($EtOH/H_2O$). Yield: (265 mg), 83%, m.p.: 199–200 °C. IR: (KBr, $\nu = \text{cm}^{-1}$) 3130 (NH), 2223 (CN), 1130 (C=S); ^{1}H-NMR: (DMSO, $\delta =$ ppm) 7.21–7.79 (m, 11H, Ar-H, and thiine γ-proton), 12.31 (s, 1H, NH); MS $m/z = 320$ (M^+, 40%), 292 (70%), 243 (55), 229 (65%), 197 (31%), 169 (54%), 137 (22%). Calcd. for $C_{18}H_{12}N_2S_2$ (320.43): C, 67.47; H, 3.77; N, 8.74; S, 20.01; found: C, 67.42; H, 3.74; N, 8.70; S, 19.92.

3.8. *5-Cyano-3-phenyl-6-(4-hydroxyphenylamino)thiine-2-thione (23b)*

Brown powder from ($EtOH/H_2O$). Yield: (260 mg), 77%, m.p.: 235–236 °C. IR: (KBr, $\nu = \text{cm}^{-1}$) 3350 (OH), 3137 (NH), 2229 (CN), 1137 (C=S); ^{1}H-NMR: (DMSO, $\delta =$ ppm) 7.10–7.82 (m, 10H, Ar-H, and thiine γ-proton), 8.22 (s, 1H, OH), 13.01 (s, 1H, NH); MS $m/z = 336$ (M^+, 44%), 304 (54%), 276 (67%), 171 (77%), 94 (50%). Calcd. for $C_{18}H_{12}N_2OS_2$ (336.43): C, 64.26; H, 3.60; N, 8.33; S, 19.06; found: C, 64.22; H, 3.55; N, 8.30; S, 19.00.

3.9. *5-Cyano-3-phenyl-6-(4-methylphenylamino)thiine-2-thione (23c)*

Orange crystals from (EtOH). Yield: (255 gm), 76%, m.p.: 220–221 °C. IR: (KBr, $\nu = \text{cm}^{-1}$) 3130 (NH), 2225 (CN), 1135 (C=S); ^{1}H-NMR: (DMSO, $\delta =$ ppm) 2.55 (s, 3H, CH_3), 7.01–7.90 (m, 10H, Ar-H, and thiine γ-proton), 13.12 (s, 1H, NH); MS $m/z = 334$ (M^+, 46%), 292 (92%), 246 (69%), 201 (76%), 142 (53%), 89 (100%), 60 (100%). Calcd. for $C_{19}H_{14}N_2S_2$ (334.46): C, 68.23; H, 4.22; N, 8.38; S, 19.17; found: C, 68.18; H, 4.10; N, 8.31; S, 19.08.

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