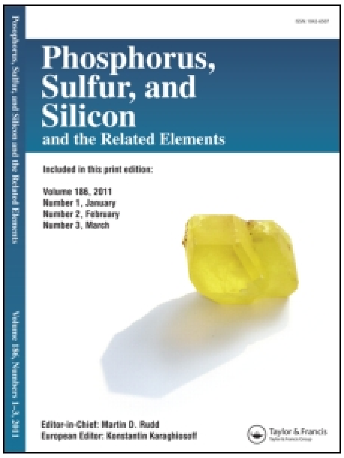

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Ring-Opening Ringn-Closure of 4-Phenyl-1,2-Dithiole-3-Thione. Novel Synthesis of Thio-Pyrano[2,3-B]Pyrane Derivatives

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RING-OPENING RINGN-CLOSURE OF 4-PHENYL-1,2-DITHIOLE-3-THIONE. NOVEL SYNTHESIS OF THIO-PYRANO[2,3-b]PYRANE DERIVATIVES

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1,2-Dithiole-3-thione (**1**) react with a number of selected α, β-unsaturated nitriles to give thiopyrano[2,3-**b**]pyrane (**3 a,b**) and / or pyridine (**3c**) derivatives in excellent yields. The products result from a ring-opening ring-closure reaction and a concomitant nucleophilic attack at the 5-position of the dithiole ring.

Keywords: Thiopyrano[2,3-b]pyrane (pyridine); 1,2-dithiole-3-thione; α, β-unsaturated nitriles

The reactions of 1,2-dithiole-3-thiones with various reagents have been reported[1–3]. It is known that 1,2-dithiole-3-thiones react with active methylene compounds to give 1,2-dithiole-3-yildene derivatives *via* a generation of hydrogen sulfide[4]. In order to find out the limitation of this reaction we investigated the reaction with selected α, β-unsaturated nitriles incorporating active methylene compounds. This was also done in continuation of our previous work toward exploring a mild synthetic procedure for the preparation of new heterocycles with possible biological activity[5–9]. Thus, 4-phenyl-1,2-dithiole-3-thione (**1**) is allowed to react with 1,1-dicyano-2-methyl-3-ethoxycarbonyl-1-propene (**2a**) and / or1-cyano-1,3-diethoxycarbonyl-2-methyl-1-propene (**2b**) in refluxing ethanolic piperidine solution to afford thiopyrano[2,3-**b**]pyrane (**3a, b**) and / or pyridine (**3c**), (***c.f. Scheme 1***). The structures of the products (**3a-c**) were established

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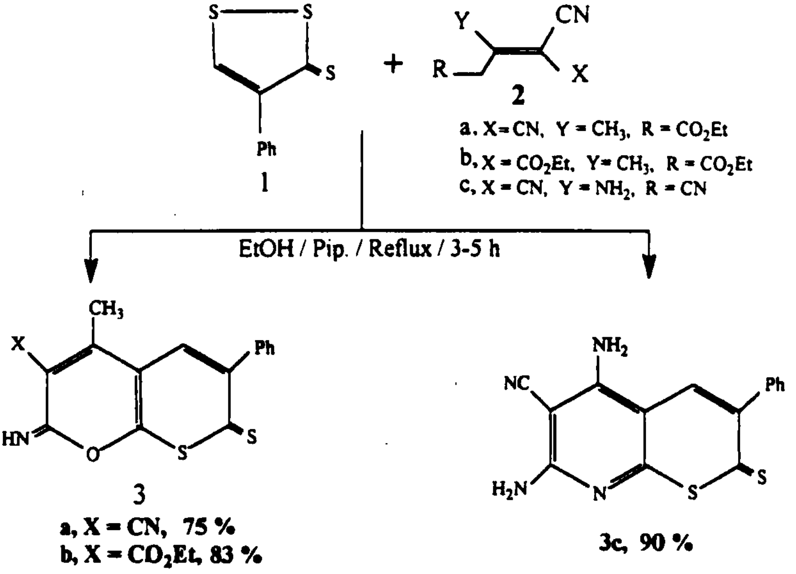
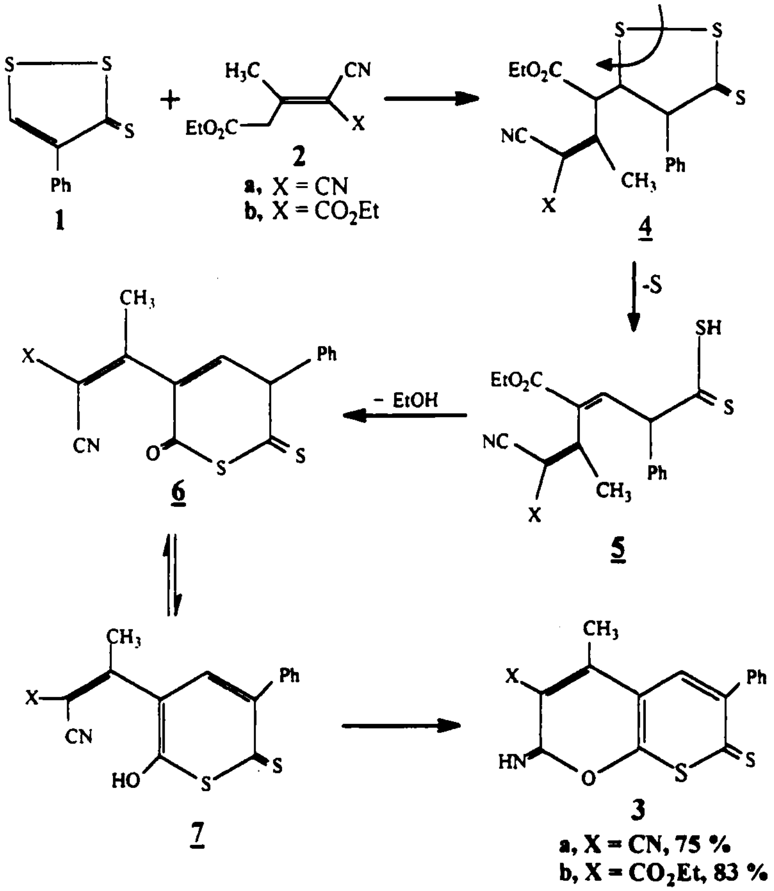
based on elemental analysis and spectral data. The **IR** spectrum (KBr, $\nu = cm^{-1}$) of (**3a**) showed characteristic bands at ν = 3212–3124 (NH), 2220 (CN) and at 1124 cm^{-1} (C=S), respectively. The ^{1}**H-NMR** spectrum (DMSO-d_6, δ = ppm) of (**3a**) exhibited in addition to the aromatic proton region (7.1–7.8) two singlet signals due to the methyl protons (δ = 1.2), and at δ = 5.2 ppm for the NH-group. The mass spectrum of (**3a**) showed m/z at 310 (M^+) and the base peak at 142, whereas the mass spectrum of (**3b**) showed m/z (M^+) at 357 and its base peak at 244.



SCHEME 1

Formation of (**3a,b**) is assumed to proceed *via* the addition of the active methylene of the α, β-unsaturated nitriles (**2a,b**) to C-5 to the dithiole (**1**) to yield the Michael adduct **4**which loses one sulfur atom in a ring-opening reaction to afford **5** which subsequently recyclizes to **6** *via* ethanol elimination and a simultaneous nucleophilic addition into 7-imino-5-methyl-3-phenyl-2-thioxothiopyrano[2,3-**b**]pyrane derivatives (**3a,b**), (*c.f.* **Scheme 2**). On the other hand, treatment of the dithiole (**1**) with 2-amino-1,1,3-tricyanopropene (**2c**) in refluxing ethanol in the presence of a catalytic amonut of piperidine afforded the corresponding

5,7-diamino-6-cyano-3-phenyl-2-thioxothiopyrano[2,3-**b**]pyridine (**3c**) in 90 % yield. The **IR** spectrum of (**3c**) showed bands at ν = 3367–3182, 2206 (CN), 1285 cm^{-1} (C=S). The ^{1}**H-NMR** spectrum revealed signals at δ = 6.2, 6.4 (2 NH_2), 7.1–7.8 (Ar-H). The mass spectrum of (**3c**) showed m/z at 311 (M+1) and the base peak at 156. Formation of (**3c**) is also believed to proceed *via* the intermediacy of the Michael adduct **8**, which upon elimination of sulfur afforded **9** and cyclizes to the thiopyrane **10**. It then underwent double cyclization to yield the final product (**3c**), (*c.f.* **Scheme 3**).



SCHEME 2

EXPERIMENTAL

Melting points reported are uncorrected. The IR spectra (KBr wafer, v = cm^{-1}) were recorded on a Shimadzu 408 and a Pye Unicam Spectrophotometer, and the ^{1}**H-NMR** spectra were recorded on a Varian EM-390–90 MHz Spectrometer with DMSO-d_6 as solvent and TMS as internal reference. The chemical shifts are expressed in δ ppm. The mass spectra were obtained by a Mass Spectrometer MS 9 (AET) El Mode. Elemental analysis were obtained from Microanalytical Center at Cairo University, Cairo, Egypt.

4-Phenyl-1,2-dithiole-3-thione (1):

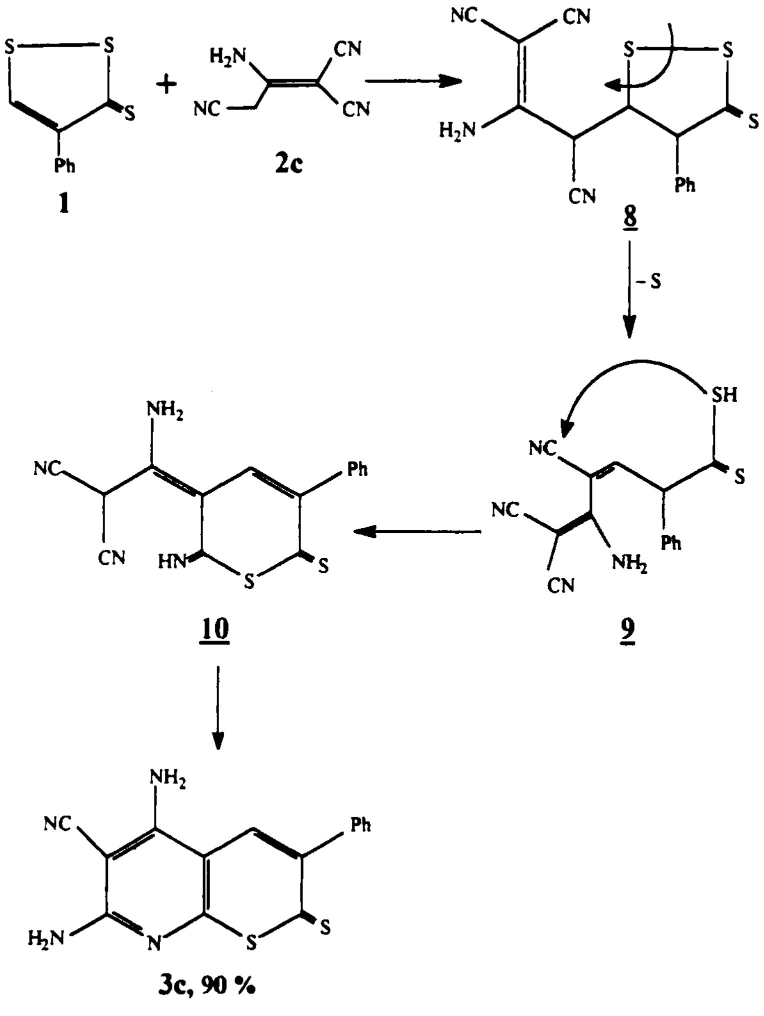
The title compound was prepared in analogy to the reported method[10]. A suspension of sulfur (3 gm atom) and potassium hydroxide (0.028 gm, 0.0005 mol) in α-mehtylstyrene (11.8 gm, 0.1 mol) was heated under reflux at 156°C for 12 h. The reaction mixture was allowed to stand in a refrigerator over night, whereupon the resulting precipitate was filtered, washed with carbon tetrachloride, recystallized from CCl_4 and dried. Yield: 12 g (57 %), m.p.: 120°C (Lit. 120)[10].

6-Cyano-7-imino-5-methyl-3-phenyl-2-thioxothiopyrano[2,3-b]-pyrane (3a)

To a mixture of the dithiole **1** (2.1 gm, 0.01 mol) and the nitrile **2a** (1.8 gm, 0.01 mol) in 30 ml ethanol an 0.5 ml of piperidine was added. The solution 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 yellow crystals in 75 % yield (2.3 gm). M.p.: 223–25°C. **IR** (KBr, v = cm^{-1}): 3212–3124 (NH), 2220 (CN), 1124 (C=S). ^{1}**H-NMR** (DMSO, δ = ppm): 7.1–7.8 (m, 6H, Ar-H), 5.2 (s, 1H, NH), 1.2 (s, 3H, Me). **MS**, m/z = 308 (M-2, 18 %), 247 (14 %), 156 (10 %), 142 (100 %), 123 (8 %). Calcd. for $C_{16}H_{10}N_2OS_2$ (310.39): C 61.91, H 3.25, N 9.03, S 20.66; Found: C 61.75, H 3.09, N 8.92, S 20.54

6-Ethoxycarbonyl-7-imino-5-methyl-3-phenyl-2-thioxothiopyrano-[2,3-b]pyrane (3b)

An ethanolic solution (30 ml) containing **1** (2.1 gm, 0.01 mol), **2b**(2.3 gm, 0.01 mol) and 0.5 ml of piperidine was refluxed for 5 h (monitored by



SCHEME 3

TLC). The solvent was evaporated in vacuo and the solid product so formed was filtered and washed with cold ethanol. After recrystalliztion from dioxane it yielded **3b** as orange crystals in 83 % yield (3 gm). M.p.: 230–32°C. **IR**: 3220–3121 (NH), 1730 (CO), 1200 (C=S). ^{1}**H-NMR** (DMSO, δ = ppm): 1.1 (t, 3H, CH_3-CH_2-), 1.3 (s, 3H, Me), 4.1 (q, 2H,

-CH_2-), 7.1–7.7 (m,.6H, Ar-H). **MS**, m/z = 357 (M^+, 35 %), 312 (10 %), 290 (25 %), 262 (45 %), 244 (100 %), 201 (22 %), 189 (55 %), 172 (40%), 145 (60 %). Calcd. for $C_{18}H_{15}NO_3S_2$ (357.44): C 60.48, H 4.23, N 3.92, S 17.94; Found: C 60.35, H 4.06, N 3.75, S 17.83

5.7-Diamino-6-cyano-3-phenyl-2-thioxothiopyrano[2,3-b]pyridine (3c)

A suspension of **1** (2.1 gm, 0.01 mol), 2-amino-1,1,3-tricyanopropene **2c** (1.3 gm, 0.01 mol) and 0.5 ml of piperidine was refluxed in 30 ml ethanol for 3h. The formed solid product was collected by filtration, washed with cold ethanol and recrystallized from DMF to give red crystals in 90 % yield, (2.8 gm). M.p.: 300–02°C. **IR**: 3367–3182 (NH_2), 2206 (CN), 1285 (C=S). ^{1}**H-NMR**, DHSO δ = ppm): 6.2 (s, 2H, NH_2), 6.4 (s, 2H, NH_2), 7.1–7.8 (m, 6H, Ar-H). **MS**, m/z = 311 (M+1), 240 (5 %), 184 (7 %), 156 (100 %), 112 (15 %). Calcd. for $C_{15}H_{10}N_4S_2$ (310.39): C 58.04, H 3.25, N 18.05, S 20.66; Found: C 57.86, H 3.09, N 18.20, S 20.48.

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