Studies of the Reaction of Substituted 1,2-Dithiole-3-thiones and -3-ones with Sodium Cyanide in Acetonitrile

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The reactions of substituted 1,2-dithiole-3-thiones and -3-ones with sodium cyanide, in acetonitrile, afford convenient routes to indolizine, pyrrolo[1,2-*a*]pyrazine and 4*H*-1,3-thiazin-4-one species.

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In previous papers [1,2], several mechanistic interpretations of the reactions of substituted 1,2-dithiole-3-thiones with nucleophiles (alkoxides, thiolates) were proposed. The position of attack on the dithiole-thione ring (at C-3, C-5 or S-2) depends both on the hard-soft character of the nucleophiles [3] and on the nature of the substituents at C-4 and C-5.

In order to gain a better understanding of the electrophilic tendency of the dithiolethione ring, we now turn our attention to the reactions of substituted 1,2-dithiole-3-thiones **1**, **2** and **3** and 1,2-dithiole-3-one **4** with sodium cyanide in acetonitrile.

Results and Discussion.

4-Methyl-5-(2-pyridyl)-1,2-dithiole-3-thione (**1**), 4-Ethoxycarbonyl-5-(2-pyridyl)-1,2-dithiole-3-thione (**2**) and 4-Methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione (**3**).

The progress of the reaction was followed by uv-visible absorption spectrometry. After addition of an excess of sodium cyanide (CN^-) to a solution of **1** in acetonitrile, at 35°, a decrease of the absorption bands at 435 and 310 nm, characteristic of the starting material **1**, is observed while a new band develops at 265 nm. Spectral changes show three isosbestic points at 290, 335 and 390 nm, indicating that a simple reaction has taken place. The reaction was stopped after 2 hours and the indolizine species **5** and **6** were isolated after methylation in 50 and 30% yield respectively (see experimental).

Compounds **2** and **3** behave similarly producing compounds **7**, **8**, **9** and **10**. Only, compounds **7** and **9** were formed in high yield as indicated in the Table.

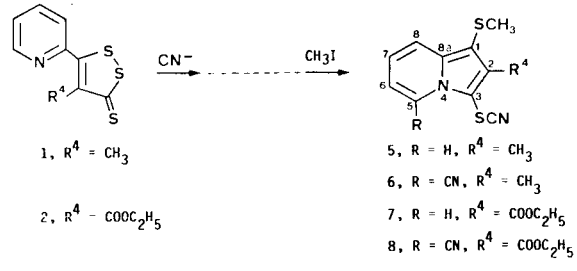
Table

Results of Nucleophilic Attack of 1,2-Dithiole-3-thiones **1**, **2** and **3** by CN^- at 35°

Starting Material	Time (minutes)	Products	Yield %
1	120	**5**	50
		6	30
2	10	**7**	80
		8	10
3	20	**9**	75
		10	5

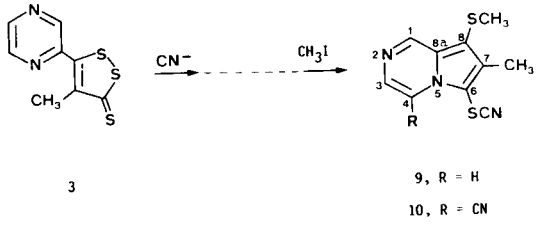
From these experimental results, it can be deduced that **1** and **2** are transformed *via* attack by CN^- at the S-2 position according to the mechanistic pathway previously reported [2] in the case of thiolates. This attack affords, after methylation, the indolizine species **5**, **6**, **7**, and **8** (Scheme 1).

Scheme 1



In the presence of CN^-, **3** yields, after methylation, the pyrrolo[1,2-*a*]pyrazine species **9** and **10** (Scheme 2).

Scheme 2

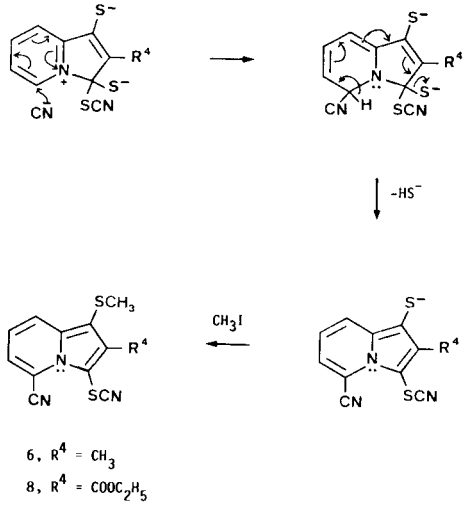


It is worth mentioning that thiolates and CN^- react similarly and afford the same kind of ring-fused products **5**, **7**, and **9**. Furthermore, CN^- is able to attack the transient ring-fused indolizinium cation at C-5 to give, after methylation, compounds **6** and **8** (Scheme 3). That CN^- is a stronger nucleophile than thiolates, under our experimental conditions, may account for the formation of **6** and **8**.

4-Methyl-5-(2-pyrazinyl)-1,2-dithiole-3-one (**4**).

After addition of an excess of CN^- to a solution of **4** in acetonitrile, at 35°, a decrease of the absorption band at 290 nm characteristic of the starting material **4** is observed and thin layer chromatography analysis indicates the

Scheme 3



6, $R^4 = CH_3$
8, $R^4 = COOC_2H_5$

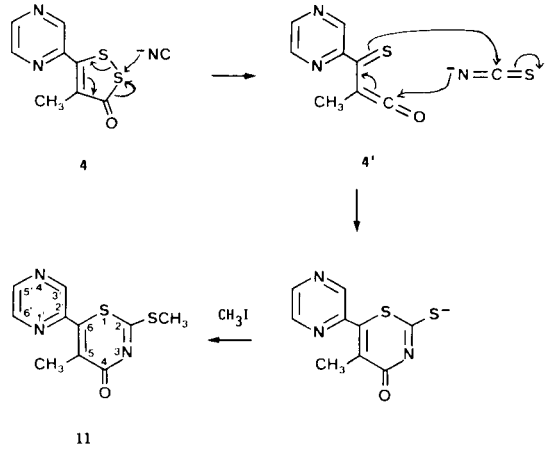
formation of several products. The reaction was stopped after 30 minutes and only the 4*H*-1,3-thiazin-4-one species **11** was isolated, after methylation, in 10% yield. Due to the available quantities, it was not possible to isolate other products.

Under the same conditions, but using an excess of thiocyanate ions (SCN^-) in addition to CN^-, (see Experimental), a new band develops at 265 nm. After methylation, the major product (60% yield) was isolated as compound **11**.

Previous experimental results suggest a nucleophilic attack at the S-2 position affording the transient ketene species **4'**. This latter species reacts with the SCN^- ion generated at the same time and produces, after methylation, the 4*H*-1,3-thiazin-4-one species **11** which has not been previously described in the literature (Scheme 4).

As the unstable transient ketene species **4'** decomposes to unknown products *via* subsequent chemical reactions,

Scheme 4



4 **4'** **11**

the yield of **11** does not exceed 10%. However, we can confirm Scheme 4 since we have isolated compound **11** as the major product (60% yield) using an excess of SCN^- in addition to CN^-. Under these conditions, **4'** is immediately transformed by SCN^- excess into compound **11**. Note that nucleophilic attack at the S-2 position can no longer occur when only SCN^- is used as nucleophile.

Finally, all these results are consistent with the following conclusions: a) As previously proved in the case of thiolate ions, cyanide ions react with 1,2-dithiole-3-thiones **1, 2** and **3** at the S-2 position to give, in high yields, the indolizine species **5, 7** and the pyrrolo[1,2-*a*]pyrazine **9**. b) Using 4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-one (**4**) as the starting material, attack by CN^- occurs at the same S-2 position, but is followed by a specific reaction step affording the 4*H*-1,3-thiazin-4-one species **11**. Compound **11** is obtained in poor yield, but the reaction proceeds in high yield in the presence of an excess of SCN^-.

EXPERIMENTAL

Substituted 1,2-dithiole-3-thiones **1, 2, 3** and -3-one **4** were supplied by Rhone-Poulenc-Santé.

The solvents used for extractions and chromatography were obtained from S. D. S. Acetonitrile, methyl iodide, sodium cyanide and sodium thiocyanate were Merck products.

The apparatus, as well as procedures, have been described elsewhere [2].

2-Methyl-1-methylthio-3-thiocyanatoindolizine (**5**) and 5-Cyano-2-methyl-1-methylthio-3-thiocyanatoindolizine (**6**).

Sodium cyanide (CN^-) (1 mmole) was added to a solution of **1** (0.1 mmole) in acetonitrile (100 ml), under nitrogen, at 35°. The reaction was allowed to go to completion (2 hours) and the resulting mixture was methylated with an excess of methyl iodide (10 mmoles). The solution was evaporated to dryness *in vacuo* at 35°. The residue was poured into water (20 ml) and then extracted with ethyl acetate (40 ml). The organic phase was dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo*.

Preparative thin layer chromatography (tlc) (hexane-acetone 10:1 v/v) provided a major product **5** (12 mg, 50% yield) and a minor product **6** (7.5 mg, 30% yield).

Compound **5** was obtained as a colourless solid with mp 85-87°; ^1H nmr (deuteriochloroform): 270 MHz, δ 2.20 (s, 3H, SCH_3 or CH_3), 2.55 (s, 3H, SCH_3 or CH_3), 6.85 (ddd, 1H, H-6, J = 7.0 Hz, J = 6.0 Hz, J = 1.5 Hz), 7.10 (ddd, 1H, H-7, J = 6.0 Hz, J = 9.0 Hz, J = 1.5 Hz), 7.65 (dd, 1H, H-8, J = 9.0 Hz, J = 1.5 Hz), 8.50 (dd, 1H, H-5, J = 7.0 Hz, J = 1.5 Hz); ms: m/z 234 (M^+), 219 (M^+-CH_3), 192 (M^+-CH_3-HCN), 78; uv (100% ACN): λ max nm (log ε) 245 (4.30), 295 (3.65, shoulder), 307 (3.75), 335 (3.55).

Anal. Calcd. for $C_{11}H_{10}N_2S_2$: C, 56.41; H, 4.27; N, 11.96; S, 27.35. Found: C, 56.38; H, 4.35; N, 11.95; S, 27.40.

Compound **6** was obtained as a yellow solid with mp 141-143°; ^1H nmr (deuteriochloroform): 270 MHz, δ 2.45 (s, 3H, CH_3 or SCH_3), 2.60 (s, 3H, CH_3 or SCH_3), 7.10 (dd, 1H, H-7, J = 9.0 Hz, J = 6.0 Hz) 7.40 (dd, 1H, H-6, J = 6.0 Hz, J = 1.5 Hz), 7.95 (dd, 1H, H-8, J = 9.0 Hz, J = 1.5 Hz); ms: m/z 259 (M^+), 244 (M^+-CH_3), 217 (M^+-CH_3-HCN), 103; uv (100% ACN): λ max nm (log ε) 255 (4.36), 305 (3.55), 317 (3.48), 395 (3.55).

Anal. Calcd. for $C_{12}H_9N_3S_2$: C, 55.60; H, 3.47; N, 16.21; S, 24.71. Found: C, 55.70; H, 3.55; N, 16.15; S, 24.65.

2-Ethoxycarbonyl-1-methylthio-3-thiocyanatoindolizine (**7**) and 5-Cyano-2-ethoxycarbonyl-1-methylthio-3-thiocyanatoindolizine (**8**).

Using the above mentioned method, **2** yielded in 10 minutes a mixture of products. Preparative tlc (hexane-acetone 3:1 v/v) provided a major product **7** (23 mg, 80% yield) and a minor product **8** (3 mg, 10% yield).

Compound **7** was obtained as a colourless solid with mp 99-101°; ^{1}H nmr (deuteriochloroform): 270 MHz, δ 1.50 (t, 3H, CH_3, ethyl), 2.40 (s, 3H, SCH_3), 4.50 (q, 2H, CH_2, ethyl), 6.95 (ddd, 1H, H-6, J = 8 Hz, J = 8 Hz, J = 1 Hz), 7.20 (ddd, 1H, H-7, J = 8 Hz, J = 10 Hz, J = 1 Hz), 7.80 (dd, 1H, H-8, J = 10 Hz, J = 1 Hz), 8.65 (dd, 1H, H-5, J = 8 Hz, J = 1 Hz); ms: m/z 292 (M^+), 277 (M^+-CH_3), 146 (M^+-CH_3-SCN-$COOC_2H_5$, 100%), 78; uv (100% ACN): λ max nm (log ε) 235 (4.36), 310 (3.74), 340 (3.60).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S_2$: C, 53.42; H, 4.11; N, 9.60; S, 21.92. Found: C, 53.50; H, 4.36; N, 9.61; S, 21.68.

Compound **8** was obtained as a yellow solid with mp 149-151°; ^{1}H nmr (deuteriochloroform): 270 MHz, δ 1.50 (t, 3H, CH_3, ethyl), 2.60 (s, 3H, SCH_3), 4.50 (q, 2H, CH_2, ethyl), 7.20 (dd, 1H, H-7, J = 8 Hz, J = 10 Hz), 7.55 (dd, 1H, H-6, J = 8 Hz, J = 1 Hz), 8.10 (dd, 1H, H-8, J = 10 Hz, J = 1 Hz); ms: m/z 317 (M^+), 302 (M^+-CH_3), 171 (M^+-CH_3-SCN-$COOC_2H_5$, 100%), 103; uv (100% ACN): λ max nm (log ε) 245 (4.36), 300 (3.60), 310 (3.55), 385 (3.60).

Anal. Calcd. for $C_{14}H_{11}N_3O_2S_2$: C, 53.00; H, 3.47; N, 13.25; S, 20.19. Found: C, 52.91; H, 3.45; N, 13.20; S, 20.23.

7-Methyl-8-methylthio-6-thiocyanatopyrrolo[1,2-*a*]pyrazine (**9**) and 4-Cyano-7-methyl-8-methylthio-6-thiocyanatopyrrolo[1,2-*a*]pyrazine (**10**).

Using the above mentioned method, **3** yielded, after 30 minutes, a mixture of products. Preparative tlc (toluene-acetone 9:1 v/v) provided a major product **9** (18 mg, 75% yield) and a minor product **10** (1.5 mg, 5% yield).

Compound **9** was obtained as a colourless solid with mp 84-86°; ^{1}H nmr (deuteriochloroform): 270 MHz, δ 2.25 (s, 3H, SCH_3 or CH_3), 2.60 (s, 3H, SCH_3 or CH_3), 7.90 (d, 1H, H-3, J = 5 Hz), 8.35 (dd, 1H, H-4, J = 5 Hz, J = 1.5 Hz), 9.10 (d, 1H, H-1, J = 1.5 Hz); ms: m/z 235 (M^+), 220 (M^+-CH_3), 193 (M^+-CH_3-HCN, 100%); uv (100% ACN): λ max nm (log ε) 240 (4.32), 296 (3.55), 307 (3.60), 340 (3.60).

Anal. Calcd. for $C_{10}H_9N_3S_2$: C, 51.06; H, 3.83; N, 17.87; S, 27.23. Found: C, 51.02; H, 3.90; N, 17.83; S, 27.20.

Compound **10** was obtained as a yellow solid with mp 139-141°; ^{1}H nmr (deuteriochloroform): 270 MHz, δ 2.45 (s, 3H, SCH_3 or CH_3), 2.65 (s, 3H, SCH_3 or CH_3), 8.35 (s, 1H, H-3), 9.20 (s, 1H, H-1); ms: m/z 260 (M^+), 245 (M^+-CH_3), 218 (M^+-CH_3-HCN); uv (100% ACN): λ max nm (log ε) 250 (4.34), 305 (3.55), 315 (3.48), 390 (3.55).

Anal. Calcd. for $C_{11}H_8N_4S_2$: C, 50.77; H, 3.08; N, 21.54; S, 24.61. Found: C, 50.73; H, 3.18; N, 21.52; S, 24.75.

5-Methyl-2-methylthio-6-(2'-pyrazinyl)-4*H*-1,3-thiazin-4-one (**11**).

The above mentioned method, with **4** = 0.1 mmole, CN^- = 0.4 mmole and methyl iodide = 10 mmoles, yielded, after 30 minutes, a mixture of products. Preparative tlc (toluene-acetone 8:2 v/v) enabled the separation of compound **11** as a colourless solid (2.5 mg, 10% yield, mp 136-138°); ^{1}H nmr (deuteriochloroform): 270 MHz, δ 2.30 (s, 3H, CH_3 or SCH_3), 2.75 (s, 3H, CH_3 or SCH_3), 8.55 (d, 1H, H-6', J = 2.5 Hz), 8.60 (d, 1H, H-3', J = 1.0 Hz), 8.80 (dd, 1H, H-5', J = 1.0 Hz, J = 2.5 Hz); ms: m/z 251 (M^+), 236 (M^+-CH_3), 178 (M^+-SCH_3-CN), 150, 123; uv (100% ACN): λ max nm (log ε) 265 (4.20), 290 (3.95, shoulder), was in agreement with previous data [4].

Anal. Calcd. for $C_{10}H_9N_3OS_2$: C, 47.81; H, 3.58; N, 16.73; S, 25.50. Found: C, 47.90; H, 3.70; N, 16.70; S, 25.47.

Using an excess of SCN^- (2 mmoles) in addition to CN^- (0.4 mmole), the previous method yielded after 30 minutes a mixture of products. Preparative tlc (toluene-acetone 8:2 v/v) provided compound **11** as the major product (15 mg, 60% yield).

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