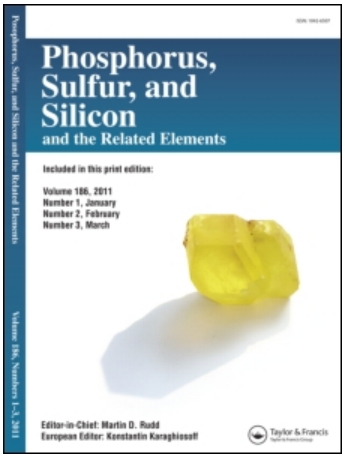

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1-(DITHIOLYLIDENE)-1-CYANOACETOPHENONES FROM DITHIOLETHIONE-BROMINE ADDUCTS WITH ENAMINONITRILES

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Title compounds are easily prepared by reaction of dithiolethione-bromine adducts with enaminonitriles followed by treatment with triethylamine. The mechanism that accounts for their formation is discussed.

Key words: 1,2-Dithiole-3-thiones; 1,3-dithiole-2-thiones; 1-(1,2-dithiol-3-ylidene)-1-cyanoacetophenones; 1-(1,3-dithiol-2-ylidene)-1-cyanoacetophenones; 3-amino-3-arylpropenenitriles.

1-(1,2-Dithiol-3-ylidene)-1-cyanoacetophenones **1** and numerous other structurally related dithiolylidene ketones have been the subject of extensive studies in relation to the geometry of their ketonic portion and valence tautomerism.[1] Their preparation has been essentially accomplished following two procedures based on the reaction of 3-methylthio and 3-unsubstituted 1,2-dithiolium salts with 1-cyanoacetophenones.[2–4] Within our researches on the reactivity of enaminonitriles towards halogen activated thiocarbonyl compounds,[5,6] we found that they are easily obtained by reaction of bromine-adducts **3** of 1,2-dithiolethiones with 3-amino-3-arylpropenenitriles **4** followed by treatment with triethylamine.

In this paper we wish to describe these simple reactions which lead to dithiolylidene ketones **1** and discuss the mechanism that accounts for their formation.

RESULTS AND DISCUSSION

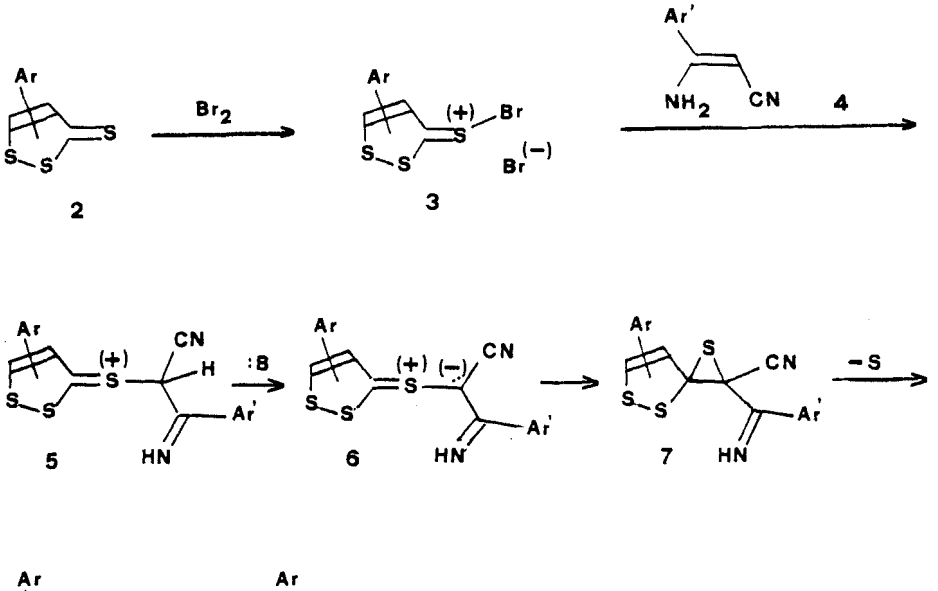
A suspension of adducts **3** in anhydrous chloroform containing a two-fold excess of enaminonitrile **4** has been kept under vigorous stirring and an atmosphere of nitrogen at room temperature for two days. The mixture was then treated with an excess of triethylamine and finally worked up to obtain a crude free of the base, its hydrobromide and solvent. Dithiolylidene ketones **1** were isolated by chromatography in yields ranging from 34 to 49% along with starting dithiolethiones **2** and enamines **4**. These latter were in part recovered as their hydrolysis products. Their structures were identified and assigned as cis-isomers on the basis of their spectral data which were identical with those reported in literature.[1,2] The two

unsubstituted terms **1a,f** were confirmed by independent synthesis based on the reactions of 1-bromo-1-cyanoacetophenone and the appropriate dithiolethione. Lower isolated yields (10–15%) of **1a,f**, however, were obtained.

Precursors of compounds **1** clearly are the imino analogs **8** which are not resistant to the hydrolytic ambient occurring during the work up of the reaction mixtures and the formation of which can be explained as illustrated in Scheme I.

The triethylamine induced deprotonation of salts **5** initially formed by attack of the enaminic β-carbon atom at the thiocarbonyl sulfur atom, generate the transient ylids **6** which afford ketones **1** through a 4π-electrocyclic closure to thiiranes **7**, followed by loss of sulfur.

This rationalization is consistent with the results of our previous investigations on the reactions of the same enaminonitriles with halogen-thioamide[5] and -isocyanate[6]



2, 3	Ar
a	5-C_6H_5
b	5-(4-$CH_3C_6H_4$)
c	5-(4-$CH_3OC_6H_4$)
d	4-C_6H_5
e	4-(4-$CH_3OC_6H_4$)

4	Ar'
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$

1, 8	Ar	Ar'
a	5-C_6H_5	C_6H_5
b	5-C_6H_5	4-$CH_3C_6H_4$
c	5-C_6H_5	4-$CH_3OC_6H_4$
d	5-(4-$CH_3C_6H_4$)	C_6H_5
e	5-(4-$CH_3OC_6H_4$)	C_6H_5
f	4-C_6H_5	C_6H_5
g	4-(4-$CH_3OC_6H_4$)	C_6H_5

SCHEME I

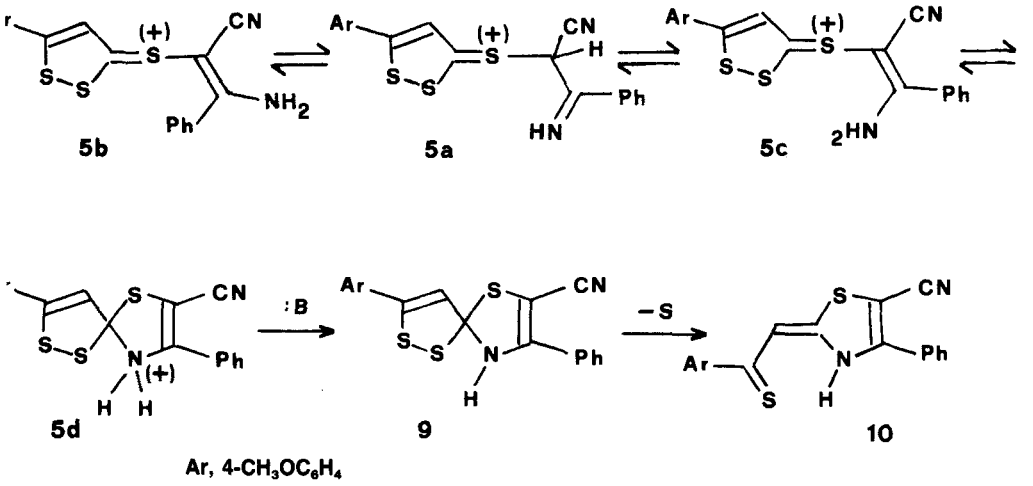
adducts from which heterocycles containing C—S bonds are formed and, furthermore, with the high electrophilic reactivity showed by sulfur of heterocyclic thioketone-bromine adducts. These give stable thiocarbonyl ylids and thione-S-imides upon treatment with carbon and nitrogen nucleophiles, respectively.[7-9] An initial transfer of bromine by adducts **3** to the enamine **4**, followed by reaction of the resulting bromoenaminonitrile and the free dithiolethione seems unlikely since an experiment carried out by adding the dithiolethione **2b** to enamine **4a** pretreated with an equivalent of bromine did not afford the expected dithiolylidene ketone **1d**. It has been found furthermore that not only 5-aryldithiolethiones, but also 4-aryl isomers, which are known to give thiopyranthiones upon treatment with enamines,[10] are inert towards enaminonitriles **4**.

The mechanism involving the replacement of halogenothio group of adduct **3** upon attack of enaminonitrile β-carbon at the thiocarbonyl carbon atom, suggested to explain the formation of 1,2-dithiole-3-imines from **3b** with amines,[11] has been rejected since only trace amounts of **1** are formed when the reaction mixtures are not treated with base.

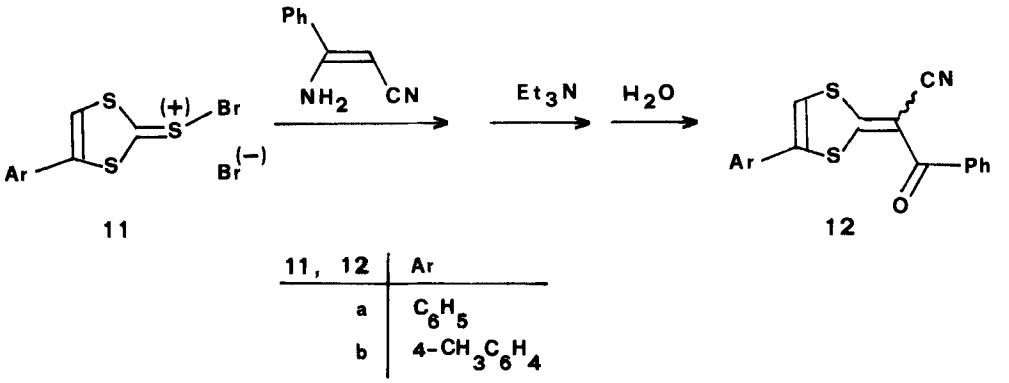
A support for the formation of salts **6** is the isolation of little amounts (3%) of 2-thiophenacylidene-thiazole **10** from the crude of a reaction conducted with adduct **3c** and **4a** under slightly refluxing chloroform for 1 hour.

For the formation of the thiazole **10** a rearrangement involving the loss of sulfur from the unisolable intermediate spirocompound **9** must be invoked. This intermediate is originated by a 6π-electrocyclic closure of the corresponding salt **5c** followed by the base induced deprotonation (Scheme II).

The structure **10** follows from the spectral data which indicate the presence of an enaminothione portion.[12] The IR spectrum shows absorptions at 2730 (broad) and 2200 cm^{-1} for the N—H and C≡N stretchings, respectively. Besides the pattern of the signals relative to the p-methoxyphenyl moiety, ^1H NMR spectrum reveals a singlet at 6.74 δ for the vinyl proton and a broad singlet at 14.22 δ for the thiazole H-3 proton. In the mass spectrum three peaks, M^+ (50%), $(M-1)^+$ (100%) and p-methoxythiobenzoyl ion (56%), dominate over the others which appear of very



SCHEME II



SCHEME III

low intensity. The assigned structure was furthermore supported by the following observations which have allowed to rule out the also conceivable structure **8e**, precursor of **1e**. Compound **10** does not undergo acid hydrolysis to **1e** and does not give the corresponding 1,6,6a,λ^4-trithiapentalene upon treatment with phosphorus pentasulfide. The very low yield of **10** can be attributed to the low concentration of the cyclic cation **5d** present in the equilibrium conditions of the refluxing solvent. From the reaction of **3e** with **4a** under the same conditions the corresponding thiazole was not found. This, however, was not surprising since a notoriously unstable thial should be formed.

Bromine-adducts **11a,b** of 1,3-dithiole-2-thione react with enamino-nitrile **4a** to give 1-(1,3-dithiol-2-ylidene)-1-cyanoacetophenones **12a,b** in ca. 40% isolated yields (Scheme III). These latter were obtained as mixtures of the two geometrical isomers as evidenced by their ^{1}H NMR spectra, which show two very close singlets in the range 7.30–7.32 δ assignable to the dithiole ring H-5 proton.[13–14] The term **12a** was also obtained as a mixture of the two geometrical isomers from an independent synthesis carried out with the corresponding dithiolethione and 1-bromo-1-cyanoacetophenone.

Even if the here described procedure affords isolated yields of compounds **1** somewhat lower than those obtainable by literature methods,[2–4] it offers the advantage of the use of readily available enaminonitriles instead of cyanoacetophenones, the preparation of which requires the dangerous manipulation of cyanide. The scope and limitations of the method are under investigation and will be reported in due course.

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer and were within ±0.4 of the theoretical values. ^{1}H NMR spectra were recorded on a Bruker WP 80 spectrometer using tetramethylsilane as internal standard and deuteriochloroform solutions. IR spectra (potassium bromide or nujol mulls) were taken on a Perkin Elmer 281 spectrophotometer, and mass spectra on a VG ZAB-2SE spectrometer. Analytical TLC was conducted on Merck silica gel 60-F_{254} precoated aluminum plates. Separation of reaction crudes were performed by column and centrifugally enhanced preparative thin layer (CTLC) chromatography using Merck silica gel H and 60-PF_{254}, respectively. Cyclohexane with increasing proportions of ethyl acetate was used as eluent.

TABLE

Physical data for dithiolylidene ketones **1a–g** and **12a,b**

Compd. no.	Ar	Ar′	Yield (%)	m.p. (°C)	Lit. m.p. (°C)	Molecular formula	Microanalysis[calc(found)]			
							C	H	N	S
1a	5-C_6H_5	C_6H_5	42	196–98	196–97[a]	$C_{18}H_{11}NOS_2$	67.26 (67.05)	3.45 (3.53)	4.36 (4.38)	19.95 (19.80)
1b	5-C_6H_5	4-$CH_3C_6H_4$	44	176–78	179–80[a]	$C_{19}H_{13}NOS_2$	68.03 (67.63)	3.91 (3.95)	4.18 (4.20)	19.12 (19.37)
1c	5-C_6H_5	4-$CH_3OC_6H_4$	40	166–68	164–66[a]	$C_{19}H_{13}NO_2S_2$	64.93 (65.25)	3.73 (3.73)	3.99 (3.98)	18.25 (18.16)
1d	5-(4-$CH_3C_6H_4$)	C_6H_5	42	181	179–80[a]	$C_{19}H_{13}NOS_2$	68.03 (68.09)	3.91 (3.84)	4.18 (3.83)	19.12 (19.33)
1e	5-(4-$CH_3OC_6H_4$)	C_6H_5	49	188–90	187–89[a]	$C_{19}H_{13}NO_2S_2$	64.93 (65.12)	3.73 (3.69)	3.99 (4.01)	18.25 (18.45)
1f	4-C_6H_5	C_6H_5	34	198–200		$C_{18}H_{11}NO_2S_2$	67.26 (67.21)	3.45 (3.55)	4.36 (4.59)	19.95 (19.81)
1g	4-(4-$CH_3OC_6H_4$)	C_6H_5	36	151		$C_{19}H_{13}NO_2S_2$	64.93 (67.15)	3.73 (3.70)	3.99 (3.72)	18.25 (18.61)
12a	4(5)-C_6H_5	C_6H_5	38	190–92	190–91[b]	$C_{18}H_{11}NOS_2$	67.26 (67.54)	3.45 (3.44)	4.36 (4.37)	19.95 (19.58)
12b	4(5)-(4-$CH_3C_6H_4$)	C_6H_5	42	196–98		$C_{19}H_{13}NOS_2$	68.03 (68.17)	3.91 (3.87)	4.18 (4.45)	19.12 (19.03)

[a]See Ref. 2.
[b]See Ref. 13.

The identification of samples from different experiments was secured by mixed m.p.s. and/or superimposable IR spectra.

Starting materials. Dithiolethiones **2** (4-[15] and 5-aryl-1,2-dithiole-3-thiones[16] and 4-aryl-1,3-dithiole-2-thiones[17]) were prepared following literature procedures. Unsubstituted enaminonitrile **4a** was purchased from Aldrich and used as received, while the methyl and methoxy derivatives **4b,c** were obtained according to the previously described procedure.[18] Bromine and chloroform were purified and dried following literature methods.[19]

Preparation of bromine-dithiolethione adducts **3**. Adducts **3** were prepared following a known procedure.[11] To a stirred solution of dithiolethione **2** (5 mmol) in carbon tetrachloride (30 ml) 0.8 (5 mmol) of bromine dissolved in the same solvent (20 ml) were dropwise added. The formed solid was collected and washed three times with 5 ml of carbon tetrachloride. They were used without further purification because they suffer extensive decomposition on attempted crystallization.

General procedure for the reaction of adducts **3** *with enaminonitriles* **4**. To a stirred solution of the adducts **3** (5 mmol) in anhydrous chlorofom (25 ml) a solution of enaminonitrile **4** (10 mmol) in the same solvent (25 ml) was added under an atmosphere of nitrogen. A vigorous stirring was kept for 48 hours and then an excess of triethylamine was added. After 30 min the mixture was repeatedly washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was chromatographed to give in the order: dithiolethione **2**, dithiolylidene ketone **1**, 1-cyanoacetophenone corresponding to the starting enamine **4** and this latter. Dithiolylidene ketones **1a–g** and **12a,b** were isolated in the yields reported in the Table. They showed typical spectral evidences. IR spectra of compounds **1a–g** do not exhibit the usual carbonyl bands in the range 1640–1720 cm^{-1} region, but absorptions in the 1548–1559 cm^{-1} region in agreement with literature.[1] The carbonyl band of isomers **12a,b** appears at 1600 cm^{-1}.[13,14] IR spectra of all cyano ketones show an absorption band at 2200 cm^{-1} for the cyano group. Besides the signals relative to the protons of aryl substituents, ^1H NMR spectra of **1a–g** show multiplets for aromatic protons which cover the signal of the dithiole ring proton. In the spectra of 1,3-dithiol-2-ylidene ketones **12a,b** two close singlets occurring in the 7.30–7.32 δ range are well distinct and assignable to the dithiole H-5 proton.[13,14] They are consistent with the existence of two geometrical isomers. Mass spectra are characterized by intense molecular ions (ca. 70%) and benzoyl ions as base peaks. Other fragment ions, but less abundant, are $(M\text{-}PhCO)^+$, $(M\text{-}Ar)^+$, and $(Ar)^+$. Peaks of modest intensity corresponding to thiobenzoyl ions are also present in the mass spectra of 5-aryl-1,2-dithiol-3-ylidene derivatives **1a–e**.

2-(4-Methoxythiophenacylidene)-4-phenyl-5-cyano-3H-thiazole **10**. Thiazole **10** was isolated in 3% yield along with dithiolylidene ketone **1e** (28%) from the crude of a reaction carried out with adduct **3c** (5 mmol) and enaminonitrile **4a** (10 mmol) in slightly refluxing chloroform (50 ml) for 1 hour and worked up, after cooling, as above reported: m.p. 184–186 °C; IR (KBr) ν_{max}: 2730br (NH), 2200 (CN) cm^{-1}: ^1H NMR ($CDCl_3$) δ: 3.82 (s, 3H, methoxyl-H), 6.70 (s, 1H, vinyl-H), 6.84 (dd, 2H, aromatic-H), 7.93 (dd, 2H, aromatic-H), 14.22 (sbr, 1H, NH); MS (*m/z*): 350 (M^+, 50%), 349 [$(M\text{-}1)^+$, 100%], 151 ($MeOPhCS^+$, 56%).
Anal. Calcd. for $C_{19}H_{14}N_2OS_2$: C, 65.12: H, 4.03; N, 7.99; S, 18.30. Found: C, 65.41; H, 3.99; N, 7.80; S, 18.25.

General procedure for the independent synthesis of dithiolylidene ketones **1a,f** *and* **12a**. A solution of bromine (0.8 g, 5 mmol) in chloroform (10 ml) was dropwise added during 10 min to a stirred solution of 1-cyanoacetophenone (0.75 g, 5.2 mmol) in the same solvent (10 ml). After 45 min the solution was washed with aqueous Na_2CO_3, dried and evaporated under reduced pressure to give an oil (1 g) shown by ^1H NMR to contain 1-bromo-1-cyanoacetophenone (70%). A solution of this oil and an equivalent amount of the appropriate dithiolethione in chloroform (20 ml) was kept all night under stirring at room temperature and then treated with an excess of triethylamine. The work up of the resulting mixture followed by CTLC gave (dithiolylidene)ketones **1a**, **1f** and **12a** in 12, 10 and 15% yield, respectively.

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