Reactions of Thioacylketene Thioacetals and *o*-Thioquinone Methides with Enamines

Renji Okazaki, Fumio Ishii, and Naoki Inamoto

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Tokyo 113

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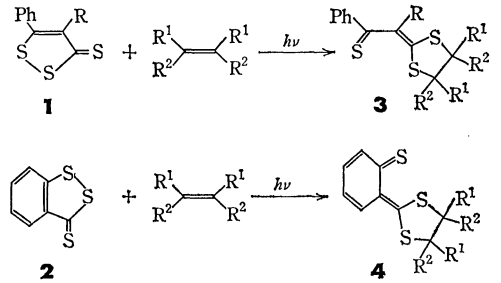
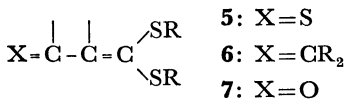
o-Thioquinone methide reacted with enamines to give [4+2] cycloadduct in good yield. In the case of morpholinoenamine, 1 : 2 adduct was obtained. Thiobenzoylketene thioacetals underwent dimerization accompanied by concomitant desulfurization upon reaction with 1-(1-pyrrolidinyl)cyclohexene. The reaction mechanism of these reactions were discussed. Some other reactions of thioacylketene thioacetals with enamines were also described.

1,2-Dithiole-3-thiones (**1**) and (**2**) photochemically react with olefins to give α-thioacylketene thioacetals (**3**) and (**4**) respectively in good yields, the latter thioacylketene thioacetal (**4**) (*i. e.*, *o*-thioquinone methide) existing as an equilibrium mixture with the dimer in solution.[1,2]



We became interested in the reactivities of these conjugated thioacetals because very few reactions have been reported on compounds of this type inspite of recent intensive studies on vinylketene (**6**)[3] and α-keto ketene thioacetals (**7**).[4]

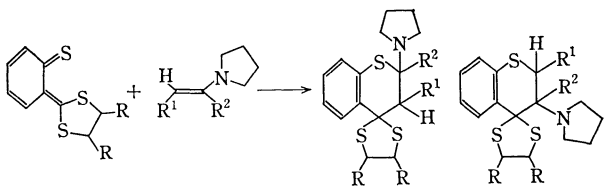


5: X=S
6: X=CR_2
7: X=O

Reactions of **3** and **4** with some electron-deficient olefins and acetylenes have been reported.[2,5] This paper gives a full account of the reactions of **3** and **4** with an electron-rich olefin, enamine.[6]

Results and Discussion

Reactions with o-*Thioquinone Methides.* *o*-Thioquinone methide (**8**) reacted with excess enamines (**9a—c**) in refluxing acetonitrile to give 1:1 adducts (**10**). Of two possible structures for the cycloadduct, **11** was eliminated by the fact that desulfurization of **10c** with Raney-nickel resulted in the formation of 2-methyl-1-phenyl-3-(1-pyrrolidinyl)propane.



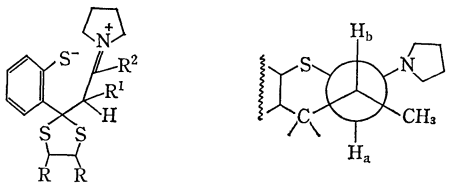
8 **9** **10** **11**

RR=$(CH_2)_4$

10a: $R^1R^2=(CH_2)_3$ 77%
10b: $R^1R^2=(CH_2)_4$ 47%
10c: R^1=Me, R^2=H 62%

It is reasonably assumed that the orientation in the cycloaddition of **9a** and **9b** is the same as that of **9c**; the products from them would thus be **10a** and **10b**, respectively.

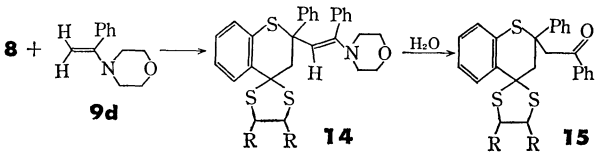
The reaction probably proceeds *via* a zwitterionic intermediate **12** followed by cyclization.



12 **13**

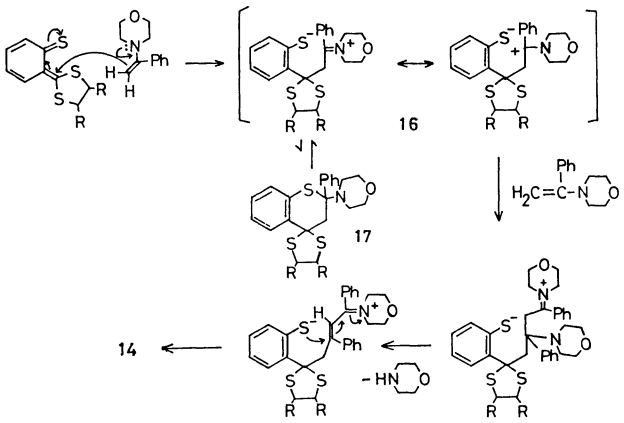
The NMR spectrum of **10c** shows a doublet (J= 10.0 Hz) at δ 4.66 attributable to H_a (see **13**). The large J value is compatible only with the configuration **13**. The formation of **13** can be explained by the cyclization of the intermediate **12** to **10** with the most stable configuration.

Enamine (**9d**) reacted with **8** in a different way from **9a—c** to afford a 1 : 2 adduct(40%), the orientation of which is presumably as shown in **14** by analogy with that of **10**. Enamine (**14**) was hydrolyzed to give ketone (**15**) upon chromatographic purification.



9d **14** **15**

The formation of **14** can be explained as depicted in Scheme 1.



Scheme 1.

The formation of the 1:2 adduct only in the case of **9d** would be due to the enhanced stabilization of the carbocation center of **16** caused by the phenyl group. Since 1:1 adduct **17** could be subjected to cleavage because of the stabilization, **16** could be attacked by another enamine followed by the elimination of morpholine and cyclization to give **14**.

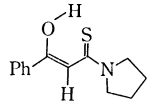
Reactions with Thioacylketene Thioacetals. Thiobenzoylketene thioacetals (**3a—c**) reacted with 1-(1-pyrrolidinyl)cyclohexene (**9b**) to give 2,3-diphenylbutane derivatives (**18**) (in refluxing acetonitrile for 10—20 h).

3a: R^1=Ph, R^2R^2=$(CH_2)_4$ **18a**: 48%
3b: R^1=H, R^2R^2=$(CH_2)_4$ **18b**: 24%
3c: R^1=CH_3, R^2=H **18c**: 4%

The structure of **18** was determined by spectral data and elemental analyses. Although mass spectra of the products show a weak or no parent peak, a very strong peak of half the parent peak always appears, suggesting a symmetric structure such as **18**. An intensive peak due to $[PhCH\text{-}C(R)=C=S]^+$ was also observed in each compound. The NMR spectra also support the structure **18**.

In the case of the reaction of **3b** with **9b**, two isomeric products **18b** (18%, mp 160—161 °C) and **18b'** (6%, mp 217—238 °C) were obtained. They show the same fragmentation pattern in the mass spectra, their IR spectra being nearly the same. It was impossible to measure the NMR spectrum of the isomer with a higher melting point because of poor solubility. These observations suggest that they are *meso*- and *dl*-compounds. In view of the fact that the *dl*-isomer has a lower melting point and higher solubility,[7] **18b** with a lower melting point and higher solubility was tentatively assigned to a *dl*-isomer and hence **18b'** with a higher melting point and lower solubility to a *meso*-isomer.

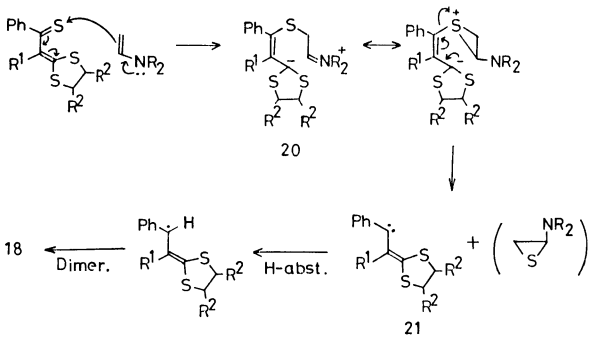
In this reaction thioamide **19** (4%) was also obtained in addition to **18b** and **18b'**. Since **19** was produced from **3b** and pyrrolidine under similar conditions, **19** obtained in the enamine reaction seems to be formed as a by-product from the reaction of **3b** with pyrrolidine derived from enamine.



19

The formation of **18** could be explained by an attack of an enamine on the sulfur atom of thiocarbonyl group (Scheme 2). The zwitterionic intermediate **20** thus formed would undergo fragmentation to form carbene **21** stabilized by the phenyl group which subsequently abstracts a hydrogen atom, dimerizing to give the final product **18**.

The ground state of vinylcarbene is triplet and capable of abstracting hydrogen atom of allylic position,[8] supporting the mechanism in Scheme 2.



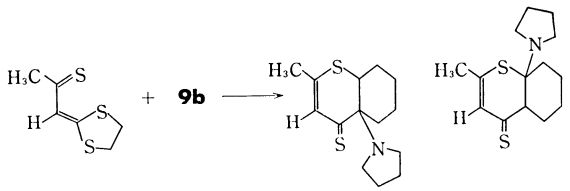
Scheme 2.

This is the first observation that an enamine can attack the sulfur atom of a thiocarbonyl group (*i.e.*, "thiophilic reaction") as in the case of organolithium compounds or Grignard reagents.[9-12] Phenyllithium attacks diphenyl trithiocarbonate to produce bis(phenylthio)carbene.[9,10] Carbene **21** can be regarded as a vinylog of dithiocarbene of type **22**, similarity between these two reactions being noteworthy.

$$(PhS)_2C{=}S + PhLi \longrightarrow (PhS)_3C^-Li^+ \rightleftarrows PhSLi + (PhS)_2C:$$

22

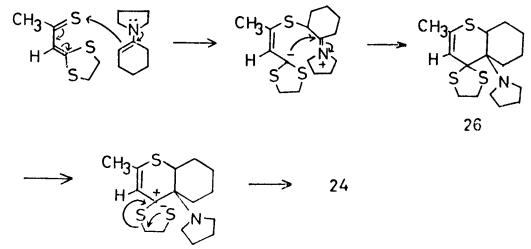
Thioacylketene thioacetal (**23**) reacted with **9b** to give conjugated thione (**24**) in 10% yield. The structure of **24** was established by its NMR and mass



23 **24** **25**

spectra and elemental analysis. The chemical shift (δ 3.20—3.80) of a broad doublet assignable to four α-protons of the pyrrolidine ring is considerably lower than that of **10a** (δ 2.5—2.9), **10b** (δ 2.4—2.9), and **10c** (δ 2.5—3.0). The lower chemical shift of **24** could be explained in terms of magnetic anisotropy of the thiocarbonyl group, suggesting structure **24** rather than **25**. The demonstrated thiophilicity described above of **3a—c** is also evidence for **24**.

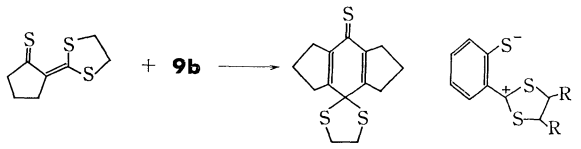
The formation of **24** can be accounted for by Scheme 3. The heterolytic cleavage of the C–S bond in **26**



Scheme 3.

might be supported by such factors as stability of the carbocation formed, participation of α-nitrogen, and high polarity of the solvent.

No reaction of 2-(1,3-dithiolan-2-ylidene)cyclopentanethione (**27**) and enamine **9b** took place in refluxing acetonitrile for 30 h. However, the reaction in *N,N*-dimethylformamide (DMF) at 110—120 °C for 15 h led to the formation of conjugated thione (**28**) (24%).



27 **28** **29**

Elemental analysis and the mass spectrum show that the molecular formula of the product is $C_{14}H_{16}S_3$. The NMR spectrum suggests the symmetric nature of the product and the UV spectrum (225 (log ε 4.23), 329 (4.44), 468 (269), and 526 nm (1.22)) reveals the presence of a conjugated thione system. The mechanism of the formation of **28** has not been clarified as yet.

The difference in reactivity in which the attack of an enamine occurs at the sulfur atom of the thiocarbonyl group in **3** but at the β-carbon of the thiocarbonyl group in *o*-thioquinone methide (**8**), can be explained mainly in terms of a greater contribution of an ionic canonical structure **29** in the case of **8**. It would reduce the thionic nature of **8** and enhance the electrophilicity of the β-carbon.

Experimental

All the reactions were carried out under nitrogen. The IR and UV spectra were measured on Hitachi EPI-G2 and EPS-3 spectrophotometers, respectively. The NMR spectra were recorded as $CDCl_3$ solutions with a Hitachi R-24 or R-20B spectrometer, tetramethylsilane being used as an internal standard. Mass spectra were determined on a Hitachi RMU-6L mass spectrometer operating at 70 eV.

Reactions of o-*Thioquinone Methides (**8**) with Enamine (**9**).* Thione **8**(0.662 g, 2.5 mmol)[2] was suspended in dry acetonitrile (30 ml) and two or three molar excess of **9** was added in a small portion over a period of 5 min. The solution was heated to reflux and maintained at this temperature with agitation for 1—2 h. The solution turned colorless from blue. The reaction was monitored by TLC. When the reaction was complete, acetonitrile was removed *in vacuo*. The residue was recrystallized from methanol or ethanol. All the products **10** were colorless crystals.

4,4-(1,2-Cyclohexylenedithio)-2-(1-pyrrolidinyl)-2,3-trimethylenethiochroman (**10a**): 0.78 g (77%); mp 154—155 °C (EtOH); NMR: δ 1.00—2.40 (m, 18H), 2.50—2.90 (m, 4H), 2.95—3.30 (m, 1H), 3.65—4.00 (m, 2H), 7.03—7.44 (m, 3H), and 8.10—8.26 (m, 1H).

Found: C, 65.28; H, 7.38; N, 3.43; S, 23.79%. Calcd for $C_{22}H_{29}NS_3$: C, 65.46; H, 7.24; N, 3.47; S, 23.83%.

4,4-(1,2-Cyclohexylenedithio)-2-(1-pyrrolidinyl)-2,3-tetramethylenethiochroman (**10b**): 0.45 g (47%); mp 71—72 °C (MeOH); NMR: δ 0.90—2.95 (m, 25H), 3.50—4.14 (m, 2H), 6.94—7.46 (m, 3H), and 8.08—8.37 (m, 1H); MS: *m/e* 226 (12%), 184 (24), 151 (45), 105 (100), and 78 (71).

Found: C, 65.98; H, 7.68; N, 3.54; S, 23.07%. Calcd for $C_{23}H_{31}NS_3$: C, 66.14; H, 7.48; N, 3.35; S, 23.03%.

4,4-(1,2-Cyclohexylenedithio)-2-(1-pyrrolidinyl)-3-methylthiochroman (**10c**): 0.584 g (62%); mp 145—146 °C (PhH:EtOH=1:2); NMR: δ 0.86—2.44 (m, 16H), 2.44—2.98 (m, 4H), 3.43—4.15 (m, 2H), 4.66 (d, J=10.0 Hz, 1H), 6.91—7.54 (m, 3H), and 8.08—8.38 (m, 1H).

Found: C, 63.78; H, 7.23; N, 3.64; S, 25.52%. Calcd for $C_{20}H_{27}NS_3$: C, 63.61; H, 7.21; N, 3.70; S, 25.47%.

*Desulfurization of **10c** with Raney Nickel.* To 2.48 g (6.5 mmol) of **10c** was added Raney nickel[13] prepared from 25 g of Al-Ni alloy in 60 ml of ethanol. The solution was heated under reflux for 1 h. After Raney nickel was separated, the filtrate was concentrated, 10 ml of ether was added and the mixture was extracted with 50 ml of 0.1 M aq HCl. The aqueous solution was neutralized with 0.1 M aq KOH, extracted with ether, and dried over anhydrous magnesium sulfate. The solution was concentrated and the residue (0.646 g, 49%) was purified by gas chromatography (JEOL JGC-750, Versamide 900, 1 m, 125 °C) to give 2-methyl-1-phenyl-3-(1-pyrrolidinyl)propane, the structure of which is supported by the following spectral data: NMR: δ 0.88 (d, J=6.0 Hz, 3H), 1.60—3.10 (m, 13H), and 7.21 (s, 5H); MS: *m/e* 203 (M^+, 0.7%), 91 (8), and 84 (100).

*Reaction of **8** with **9d**.* To 0.709 g (2.7 mmol) of **8** in 30 ml of dry acetonitrile was added 1.90 g (10 mmol) of **9d**. The solution was heated under reflux for 6.5 h. Upon cooling, 4,4-(1,2-cyclohexylenedithio)-2-phenyl-2-(β-morpholinostyryl)thiochroman (**14**) was precipitated as colorless crystals and recrystallized from a mixture of benzene and ethanol (1:2), 0.511 g, 34%. Mp 190—191 °C; NMR: δ 1.00—2.90 (m, 14H), 3.35—3.75 (m, 4H), 3.80—4.30 (m, 2H), 4.68 (s, 1H), and 6.60—8.80 (m, 14H); MS: *m/e* 557 (M^+, 0.1%), 291 (59), and 184 (100).

Found: C, 71.20; H, 5.88; N, 2.58; S, 16.91%. Calcd for $C_{33}H_{35}NOS_3$: C, 71.05; H, 6.32; N, 2.51; S, 17.24%.

The filtrate was concentrated and subjected to dry column chromatography on silica gel with dichloromethane. 4,4-(1,2-Cyclohexylenedithio)-2-phenacyl-2-phenylthiochroman (**15**) was precipitated as colorless crystals, and recrystallized from a mixture of benzene and ethanol (1:2), yield 81 mg (6%). Mp 220—221 °C; NMR: δ 1.00—2.70 (m, 10H), 3.40—4.20 (m, 2H), 4.20—4.70 (m, 2H), and 6.90—8.70 (m, 14H); IR(KBr): 1680 cm^{-1} (C=O); MS 488 (M^+, 0.2%) and 184 (100).

Found: C, 71.11; H, 5.88; S, 19.34%. Calcd for $C_{29}H_{28}OS_3$: C, 71.27; H, 5.77; S, 19.68%.

*Reaction of **3** with **9b**.* a) To **3b**[1] (0.83 g, 3.0 mmol) in refluxing acetonitrile (30 ml) was added 2.57 g (17 mmol) of **9b** in a small portion over a period of 10 min. The solution was stirred at this temperature for 12 h. When the reaction was complete, the color of the solution turned red from deep green. Upon cooling, **18b'** (45 mg, 6%) was precipitated as colorless crystals and recrystallized from THF. The filtrate was subjected to dry column chromatography on silica gel with dichloromethane to give 2,3-diphenyl-1,4-bis(4,5-tetramethylene-1,3-dithiolan-2-ylidene)butane **18b** (0.14 g, 18%) and 3-hydroxy-*N,N*-tetramethylenethiocinnamamide **19** (30 mg, 4%), the latter being identical with an authentic sample.[14]

18b: mp 160—161 °C; NMR: δ 1.10—2.20 (m, 16H), 3.50—4.10 (m, 6H), 5.60—5.80 (dd, J=7.6 Hz, J=1.5 Hz, 2H), and 6.90—7.40 (m, 10H); MS: *m/e* 522 (M^+, 7%), 261 ($M^+/2$, 46), and 147 (100).

Found: C, 69.09; H, 6.62; S, 24.20%. Calcd for $C_{30}H_{34}S_4$: C, 68.92; H, 6.55; S, 24.53%.

18b': mp 237—238 °C; MS: *m/e* 522 (M^+, 0.9%), 261 ($M^+/2$, 36), and 147 (100).

Found: C, 68.79; H, 6.68; S, 24.56%. Calcd for $C_{30}H_{34}S_4$: C, 68.92; H, 6.55; S, 24.53%.

b) Reactions of **3a**[1] (0.280 g, 0.76 mmol) and **3c**[15] (1.89 g, 0.75 mmol) with **8b** (2.00 g, 13.2 mmol for **3a** and 3.00 g, 18.7 mmol for **3c**) were carried out in a similar way to that for **3b**.

1,2,3,4-Tetraphenyl-1,4-bis(4,5-tetramethylene-1,3-dithiolan-2-ylidene)butane (**18a**): 0.124 g, 48%; mp 244—245 °C; NMR: δ 1.10—2.40 (m, 16H), 3.50—4.10 (m, 4H), 4.30—4.60 (m, 2H), and 6.90—7.60 (m, 20H); MS: *m/e* 337 ($M^+/2$, 100%) and 223 (70).

Found: C, 74.81; H, 6.26; S, 18.63%. Calcd for $C_{42}H_{42}S_4$: C, 74.73; H, 6.27; S, 18.99%.

3,4-Diphenyl-2,5-bis(1,3-dithiolan-2-ylidene)hexane (**18c**): 60 mg, 4%; mp 260—261 °C; NMR: δ 1.84 (s, 6H), 3.30 (s, 8H), 4.58 (s, 2H), and 7.00—7.50 (m, 10H); MS: *m/e* 442 (M^+, trace), 221 ($M^+/2$, 100), and 161 (33).

Found: C, 65.41; H, 5.87; S, 28.79%. Calcd for $C_{26}H_{24}S_4$: C, 65.11; H, 5.92; S, 28.97%.

*Reaction of **23** with **9b**.* To 0.870 g (5 mmol) of **23**[15] in 30 ml of dry acetonitrile was added 3.00 g (19 mmol) of **9b** in a small portion. The reaction mixture was refluxed for 2 h. After the solvent had been removed, the residue was dissolved in benzene and chromatographed on alumina. 2-Methyl-5,6-tetramethylene-5-(1-pyrrolidinyl)-5,6-dihydro-4*H*-thiopyran-4-thione (**24**) (0.125 g, 10%) was eluted with a mixture of benzene and ethyl acetate (1:1), which was recrystallized from ethanol as yellow crystals, mp 220—221 °C. NMR: δ 1.10—2.50 (m, 12H), 2.72 (s, 3H), 3.20—3.80 (m, 5H), and 6.46 (s, 1H); MS: *m/e* 267 (M^+, 55%), 234 (39), 223 (32), 190 (47), 152 (20), and 41 (100).

Found: C, 62.70; H, 7.87; N, 5.14; S, 24.00%. Calcd for $C_{14}H_{21}NS_2$: C, 62.87; H, 7.92; N, 5.24; S, 23.97%.

*Reaction of **27** with **9b**.* To a DMF solution (30 ml) of **27**[15] (2.32 g, 11 mmol) was added **9b** (4.50 g, 30 mmol) in a small portion. After being refluxed at 110—120 °C for 15 h, the solution was poured into 50 ml of water and extracted with 100 ml of dichloromethane, the extract being dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in benzene and subjected to dry column chromatography on silica gel with dichloromethane. 4,4-(Ethylenedithio)-2,3 : 5,6-bis(trimethylene)-2,5-cyclohexadiene-1-thione (**28**) was precipitated as purple crystals, and recrystallized from a mixture of benzene and hexane (1:1), 0.363 g (24%). Mp 133—134 °C; NMR: δ 1.60—2.10 (m, 4H), 2.40—3.20 (m, 8H), and 3.46 (s, 4H); MS: *m/e* 280 (M^+, 98%), 252 (12), 220 (29), and 176 (100); UV: λ_{max} (EtOH) 225 (log ε 4.23), 329 (4.44), and 468 (2.69); λ_{max} (PhH) 526 nm (1.22).

Found: C, 59.82; H, 5.79; S, 34.60%. Calcd for $C_{14}H_{16}S_2$: C, 59.95; H, 5.75; S, 34.30%.

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