Reaction of Dichloroketene with Cyclic Thioketals of α,β-Cycloalkenones: Synthesis of 1,7-Dithiacycloalk-5-en-2-one Derivatives by a Four-Carbon Cycloenlargement

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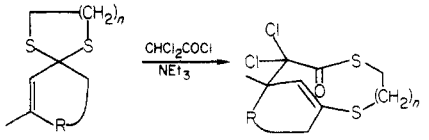
Cyclic thioketals of α,β-cycloalkenones undergo a four-carbon cycloenlargement of the 1,3-dithia *n*-membered ring by reaction with dichloroketene to give 1,7-dithiacycloalk-5-en-2-one derivatives in good yields at room temperature. A mechanistic pathway for the regioselective inclusion of the dichloroketene moiety in a formally [4 + 2] cycloaddition process is proposed. This reaction of dichloroketene is remarkable for its simplicity and appears useful for synthesis of multifunctional dithia macrocyclic systems.

The enhanced reactivity of dihalo- and alkylhaloketenes has played an ever increasing role in synthetic organic chemistry.[1-3] In particular there are several reports on the [2 + 2] cycloaddition of dichloroketene with cyclopentadienes and olefins to produce substituted α,α-dichlorocyclobutanones. These, in turn, can be readily dechlorinated with zinc or subjected to other useful transformations.[4-9]

In 1978, Malherbe and Bellus[10] described the reaction of dichloroketene with allyl ethers, allyl sulfides, and allyl selenides. They found α,α-dichlorocyclobutanones from [2 + 2] cycloaddition and also rearrangement products arising via sulfonium intermediates.

We disclose here an attractive and very efficient reaction of dichloroketene we have discovered during studies of the chemical behavior of functionalized olefins with reactive haloketenes.

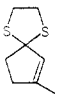
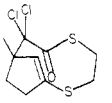
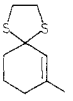
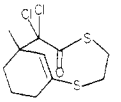
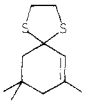
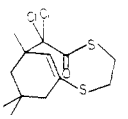
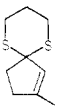
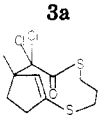
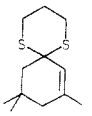
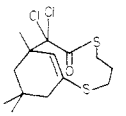
Dichloroketene, prepared in situ by dehydrohalogenation of dichloroacetyl chloride with triethylamine,[3] reacted with cyclic thioketals of α,β-cycloalkenones at room temperature in *n*-hexane. Workup of mixtures after 4 h provided *trans*-1,7-dithiacyclonon-5-en-2-one (**1a–3a**) and *trans*-1,7-dithiacyclodec-5-en-2-one (**4a–5a**) derivatives. Some results given by our process are shown in Table I where the yields refer to analytically pure products obtained by crystallization from *n*-hexane.



1-5 **1a-5a**

It is noteworthy that, in our case, α,α-dichlorocyclobutanone derivatives were not detected although IR analysis was performed on reaction mixtures (absence of CO band at 1800 cm^{-1}), and the formation of a single product was indicated by TLC examination.

Table I. Reactions of Dichloroketene with Cyclic Thioketals of α,β-Cycloalkenones

starting cyclic thioketals	products	mp, °C	% yield
 **1**	 **1a**	120-121	85
 **2**	 **2a**	93-95	80
 **3**	 **3a**	90-92	87
 **4**	 **4a**	124-126	78
 **5**	 **5a**	127-128	88

Structure Assignment.

Products **1a–5a** were shown to be 1:1 dichloroketene adducts of cyclic thioketals of α,β-cycloalkenones (**1–5**) by elemental analysis and mass spectra. Taking the dichloroketene adduct of ethylene thioketal of 3-methylcyclopent-2-en-1-one as representative, the IR spectrum of this adduct showed a strong CO absorption at 1680 cm^{-1} and a double bond stretching absorption at 1608 cm^{-1}. The ^1H NMR spectrum exhibited a multiplet for one vinylic proton and a singlet for one methyl centered, respectively, at δ 6.15 and 1.52; between δ 4.00 and 1.60 a very complex

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(2) Bak, D. A.; Brady, W. T. *J. Org. Chem.* **1979**, *44*, 107 and references cited therein.
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(4) Fletcher, V. R.; Hassner, A. *Tetrahedron Lett.* **1970**, 1071.
(5) Seebach, D.; Beckman, S.; Geiger, H. in "Methoden der Organischen Chemie (Houben-Weyl)"; Mueller, E., Ed.; George Thieme Verlag: Stuttgart, 1971; Vol. IV/4.
(6) Trost, B. M. *Top. Curr. Chem.* **1973**, *41*, 1.
(7) Trost, B. M. *Acc. Chem. Res.* **1974**, *7*, 85.
(8) Trost, B. M. *Pure* Appl. *Chem.* **1975**, *43*, 563.
(9) Greene, A. E.; Depres, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.
(10) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. We thank referees for calling our attention to this important communication.

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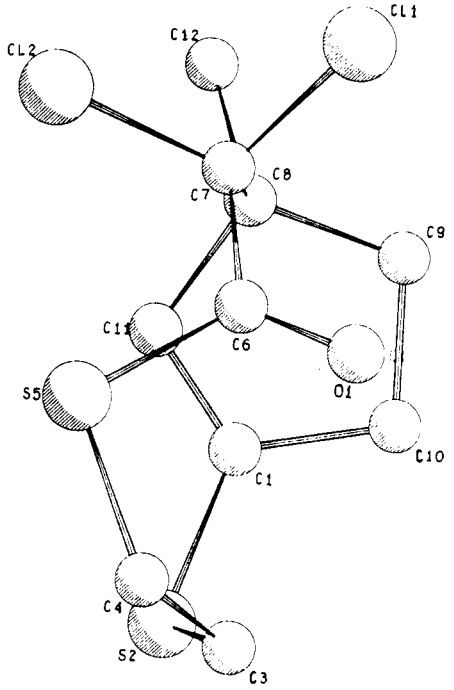
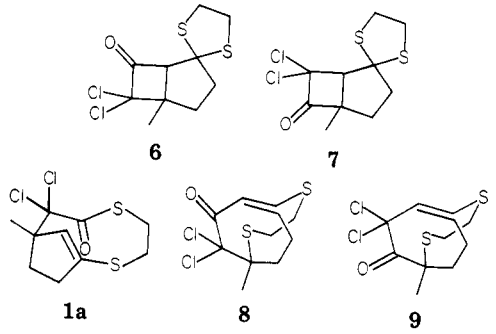


Figure 1. Perspective view of compound **1a**.

system of signals was present for a total of eight hydrogens. These spectral data readily excluded the bicyclo [3.2.0]-heptanones **6** and **7**, arising by a [2 + 2] cycloaddition of dichloroketene with cyclic thioketal **1**. They are consistent with structure **1a**, but other structures such as **8** and **9**, these also derived by hypothetical rearrangements of intermediate **6** and **7**, cannot be excluded. Nevertheless ^{13}C NMR and mass spectra did not allow unambiguously assignment of the structure.



6 **7** **1a** **8** **9**

A definitive structure was provided by X-ray diffraction analysis, which revealed the adduct to be 7,7-dichloro-2,5-dithiabicyclo[6.2.1]undec-1(11)-en-6-one (**1a**, Figure 1; for Table II and Table III see paragraph at the end of paper about supplementary material).

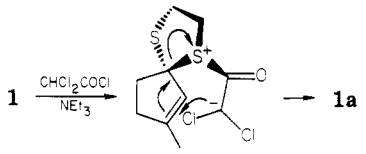
Discussion

1,3-Dithia *n*-membered rings of the starting systems (**1–5**) formally underwent a four-carbon cycloenlargement process with the regioselective inclusion of dichloroketene moiety between one sulfur atom and the remote unsaturated carbon atom.

A reasonable pathway to compounds **1a–5a** can be depicted as a two-stage reaction initiated by a nucleophilic attack of one sulfur atom at the sp carbon atom of dichloroketene to generate 1,3-dipolar intermediate **10** that undergoes a [3,3] sigmatropic rearrangement to give cycloenlarged products as shown in Scheme I.

As mentioned above, all our attempts to detect α,α-dichlorocyclobutanone derivatives from the reaction between

Scheme I



10

dichloroketene and cyclic thioketals **1–5** were unsuccessful. On the other hand, until recently the yield of cyclobutanones from the cycloaddition of dichloroketene to tri- and tetrasubstituted olefins has been low or nil. We did not use the recently described improved procedures[2,3] which overcome these difficulties; nevertheless, dichloroketene enters readily in our cycloenlargement reactions. Our results are in agreement with those reported by Malherbe and Bellus.[10]

Conclusions

As far as we are aware, synthesis of derivatives of thiaolefinic thialactones such as **1a–5a** has never been reported. This route is remarkable for its simplicity. Easily accessible starting materials are used and reactions are performed under mild conditions and are free from reaction byproducts which might interfere with easy isolation of compounds.

Experimental Section

Proton NMR spectra were recorded at 60 MHz on a Varian EM 360L instrument and at 100 MHz on a Varian XL-100 operating in the CW mode. Proton noise decoupled ^{13}C spectra were recorded at 25.15 MHz with a Varian XL-100 by the FT technique and spectral data are collected in Table IV (see paragraph at the end of paper about supplementary material). Resonance assignments were made with the aid of the off-resonance technique. Unless otherwise stated ^1H and ^{13}C shifts are given in parts per million from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Mass spectra were recorded with a Varian 112S instrument. Microanalyses were performed by using C, H, N Analyzer Model 185 from Hewlett-Packard Co. Dichloroacetyl chloride, 2,5-hexanedione, 1,2-ethanedithiol, 1,3-propanedithiol, isophorone, 3-methylcyclohex-2-en-1-one, and triethylamine are commercial materials. 3-Methylcyclopent-2-en-1-one was prepared by cyclization of 2,5-hexanedione as previously described.[11] Analytical grade solvents (Carlo Erba) were used without further purification.

Preparation of Cyclic Thioketals. General Procedure. A solution containing ketone (0.36 mol) and 1,2-ethanedithiol or 1,3-propanedithiol (0.43 mol) in chloroform (400 mL) was stirred at room temperature and boron trifluoride etherate (6 mL) was slowly added. The solution was allowed to stand at room temperature during 4–5 days and was then washed with a saturated aqueous solution of sodium carbonate (3 × 100 mL) and with brine (2 × 100 mL). The layers were separated and the resulting chloroform solution was dried (Na_2SO_4) and concentrated by distillation at atmospheric pressure, recovering chloroform in a flask containing a stirred aqueous solution of potassium permanganate. The crude mixture was distilled at reduced pressure, using a Vigreux column (20 cm).

7-Methyl-1,4-dithiaspiro[4.4]non-6-ene (1). 3-Methylcyclopent-2-en-1-one and 1,2-ethanedithiol gave **1** in 55% yield: bp 157–160 °C (30 mm); ^1H NMR δ 5.42 (m, 1 H), 3.30 (s, 4 H), 2.92–2.10 (m, 4 H), 1.72 (br s, 3 H). Anal. Calcd for $C_8H_{12}S_2$: C, 55.80; H, 7.03. Found: C, 55.87; H, 7.15.

7-Methyl-1,4-dithiaspiro[4.5]dec-6-ene (2). 3-Methylcyclohex-2-en-1-one and 1,2-ethanedithiol gave **2** in 71% yield: bp 177–181 °C (30 mm); ^1H NMR δ 5.54 (m, 1 H), 3.30 (s, 4 H), 2.60–1.40 (m, 6 H), 1.60 (br s, 3 H). Anal. Calcd for $C_9H_{14}S_2$: C, 58.05; H, 7.58. Found: C, 58.31; H, 7.67.

(11) Acheson, R. M.; Robinson, R. *J. Chem. Soc.* **1952**, 1131.

7,9,9-Trimethyl-1,4-dithiaspiro[4.5]dec-6-ene (3). Isophorone and 1,2-ethanedithiol gave **3** in 54% yield: bp 144–146 °C (8 mm); ^{1}H NMR δ 5.55 (m, 1 H), 3.32 (s, 4 H), 2.18 (s, 2 H), 1.75 (s, 2 H), 1.66 (br s, 3 H), 1.00 (s, 6 H). Anal. Calcd for $C_{11}H_{18}S_2$: C, 61.66; H, 8.47. Found: C, 61.75; H, 8.52.

8-Methyl-1,5-dithiaspiro[5.4]dec-7-ene (4). 3-Methylcyclopent-2-en-1-one and 1,3-propanedithiol gave **4** in 43% yield: bp 180–185 °C (30 mm); ^{1}H NMR δ 5.60 (m, 1 H), 3.10–1.25 (m, 8 H), 1.78 (br s, 3 H). Anal. Calcd for $C_9H_{14}S_2$: C, 58.05; H, 7.58. Found: C, 58.00; H, 7.45.

8,10,10-Trimethyl-1,5-dithiaspiro[5.5]undec-7-ene (5). Isophorone and 1,3-propanedithiol gave **5** in 64% yield: bp 156–158 °C (8 mm); ^{1}H NMR δ 5.68 (m, 1 H), 3.10–2.75 (m, 4 H), 2.15–1.60 (m, 2 H), 2.00 (s, 2 H), 1.78 (s, 2 H), 1.70 (br s, 3 H). Anal. Calcd for $C_{12}H_{20}S_2$: C, 63.13; H, 8.83. Found: C, 62.85; H, 8.78.

Cycloenlargement Reaction. General Procedure. A solution of cyclic thioketal (2.7×10^{-2} mol) and dichloroacetyl chloride (3.0×10^{-2} mol) in *n*-hexane (60 mL) was stirred at room temperature under nitrogen and a solution of triethylamine (3.3×10^{-2} mol) in *n*-hexane (20 mL) was slowly added during 1 h. After 3–4 h of reaction at room temperature dichloromethane (250 mL) and water (100 mL) were added and the brown organic layer was washed with an aqueous solution of HCl (5%, 3 × 30 mL), water (2 × 30 mL), an aqueous solution of Na_2CO_3 (5%, 3 × 50 mL), and a saturated solution of NaCl (2 × 30 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The reaction mixture was purified by crystallization from *n*-hexane and decolorized with charcoal. White crystals were collected by filtration and dried.

2,2-Dichloro-1-methyl-4,7-dithiabicyclo[6.2.1]undec-8-(11)-en-3-one (1a). Cyclic thioketal **1** gave **1a**: 6.49 g, 85% yield; mp 120–121 °C; IR (KBr) 1680 (vs), 1605 (m) cm^{-1}; ^{1}H NMR δ 6.15 (m, 1 H), 4.00–1.60 (m, 8 H), 1.52 (s, 3 H); mass spectrum, *m/e* 282 ($M^{+\cdot}$). Anal. Calcd for $C_{10}H_{12}Cl_2OS_2$: C, 42.42; H, 4.27. Found: C, 42.51; H, 4.31.

2,2-Dichloro-1-methyl-4,7-dithiabicyclo[6.3.1]dodec-8-(12)-en-3-one (2a). Cyclic thioketal **2** gave **2a**: 6.41 g, 80% yield; mp 93–95 °C IR (KBr) 1680 (vs), 1610 (m) cm^{-1}; ^{1}H NMR δ 6.40 (m, 1 H), 4.00–3.10 (m, 2 H), 3.08–2.86 (m, 2 H), 2.30–1.22 (m, 4 H), 1.36 (s, 3 H); mass spectrum, *m/e* 296 ($M^{+\cdot}$). Anal. Calcd for $C_{11}H_{14}Cl_2OS_2$: C, 44.46; H, 4.74. Found: C, 44.52; H, 4.78.

2,2-Dichloro-1,10,10-trimethyl-4,7-dithiabicyclo[6.3.1]dodec-8(12)-en-3-one (3a). Cyclic thioketal **3** gave **3a**: 7.64 g, 87%; mp 90–92 °C; IR (KBr) 1675 (vs), 1625 (w) cm^{-1}; ^{1}H NMR δ 6.32 (m, 1 H), 3.80–1.80 (m, 8 H), 1.52 (s, 3 H), 1.06 (s, 6 H); ^{1}H NMR (C_6D_6) δ 6.20 (m, 1 H), 3.50–2.78 (m, 4 H), 2.4–1.5 (m, 4 H), 1.3 (s, 3 H), 0.82 (s, 3 H), 0.70 (s, 3 H); mass spectrum, *m/e* 324 ($M^{+\cdot}$). Anal. Calcd for $C_{13}H_{18}Cl_2OS_2$: C, 48.01; H, 5.57. Found: C, 48.24; H, 5.61.

2,2-Dichloro-1-methyl-4,8-dithiabicyclo[7.2.1]dodec-9-(12)-en-3-one (4a). Cyclic thioketal **4** gave **4a**: 6.25 g, 78% yield; mp 124–126 °C; IR (KBr) 1685 (vs), 1590 (w) cm^{-1}; ^{1}H NMR δ 5.85 (m, 1 H), 3.55–1.40 (m, 10 H), 1.52 (s, 3 H); mass spectrum, *m/e* 296 ($M^{+\cdot}$). Anal. Calcd for $C_{11}H_{14}Cl_2OS_2$: C, 44.46; H, 4.74. Found: C, 4.55; H, 4.81.

2,2-Dichloro-1,11,11-trimethyl-4,8-dithiabicyclo[7.3.1]tridec-9(13)-en-3-one (5a). Cyclic thioketal **5** gave **5a**: 8.05 g, 88% yield; mp 127–128 °C; ^{1}H NMR δ 5.87 (m, 1 H), 3.72–1.22 (m, 10 H), 1.45 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H); mass spectrum, *m/e* 338 ($M^{+\cdot}$). Anal. Calcd for $C_{14}H_{20}Cl_2OS_2$: C, 49.57; H, 5.94. Found: C, 49.35; H, 5.85.

X-ray Analysis of 1a. Precise unit-cell dimensions were determined by a least-squares fit on 23 independent 2θ values. The crystal used was 0.1 × 0.6 × 0.4 mm. Crystal data: $C_{10}H_{12}Cl_2OS_2$, M = 282.0, monoclinic, space group $P2_1/n$ a = 15.138 (3) Å, b = 12.035 (2) Å, c = 6.579 (5) Å, β = 93.41 (3)°, V = 1196.5 Å^3, Z = 4, d_c = 1.57 g cm^{-3}. Intensity data were collected by a Philips 1100 diffractometer out to 240° by use of Mo Kα radiation with a graphite monocromator and with a scan speed of 0.06° s^{-1}, a scan width of 0.8°, a take-off angle of 2°, a 0.6-mm window, and a counting background for 20 s on either side of the peak. Of 1888 independent reflections, 1492 having $I > 2.5\sigma(I)$ were considered observed.

Structure Determination and Refinement. After correction for Lorentz and polarization factors of 1492 independent reflections, 1264, for which $\sin\theta \leq 0.40$, were used in the analysis. The structure was solved by direct methods with the crystallographic program system SHELX (Sheldrick, 1976); the first E map indicated positions for all the nonhydrogen atoms. Subsequent difference Fourier synthesis indicated positions for all the hydrogen atoms. The structure, except the hydrogen atoms, was refined anisotropically, using full-matrix least squares. The weighting scheme was $w = 3.2835/(\delta^2 F_{obsd} + 0.000\,131 F_{obsd}^2)$. The final coonventional agreement factor was 0.041 for 1280 reflections (R_w = 0.039; R_G = 0.041; R_M = 0.041). Drawings were made with PLUTO (Motherwell, 1976).

Acknowledgment. We gratefully acknowledge Professor Giovanni Valle, University of Padova, for intensity data collection.

Registry No. 1, 76793-90-3; **1a**, 76793-91-4; **2**, 76793-92-5; **2a**, 76793-93-6; **3**, 76793-94-7; **3a**, 76793-95-8; **4**, 76793-96-9; **4a**, 76793-97-0; **5**, 76793-98-1; **5a**, 76793-99-2; dichloroketene, 4362-56-5; dichloroacetyl chloride, 79-36-7; 3-methylcyclopent-2-en-1-one, 2758-18-1; 3-methylcyclohex-2-en-1-one, 1193-18-6; isophorone, 78-59-1; 1,2-ethanedithiol, 540-63-6; 1,3-propanedithiol, 109-80-8.

Supplementary Material Available: Data for the X-ray structure of **1a** are available as bond lengths with estimated standard deviations (Table II), bond angles with estimated standard deviations (Table III), fractional atomic coordinates with estimated standard deviations (Table V), isotropic and anisotropic thermal parameters with estimated standard deviations (Table VI), fractional atomic coordinates with estimated standard deviations (Table VII). ^{13}C NMR data for compounds **1a–5a** are available as Table IV (5 pages). Ordering information is given on any current masthead page.

General Approach to the Synthesis of Naturally Occurring δ-Lactones[1]

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The adducts from thermal and/or high-pressure Diels–Alder reactions between 1-methoxybuta-1,3-diene and carbonyl compounds (glyoxylates, aldehydes) are utilized as the starting materials for the syntheses of naturally occurring δ-lactones. Total syntheses of massoilactone, 6-phenyl-2-pyrone, and 2-methoxy-6-undecyl-5,6-dihydro-2*H*-pyran are described. A general approach to these syntheses is presented.

It has been shown[2] that butyl 2-methoxy-5,6-dihydro-2*H*-pyran-6-carboxylate (**1a**), easily obtainable via the Diels–Alder reaction of 1-methoxybuta-1,3-diene and butyl glyoxylate, can be utilized as the starting material for the

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