Application of Bisthio Carbanions to the Elaboration of 2-Cyclohexenone Systems

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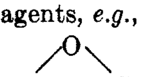
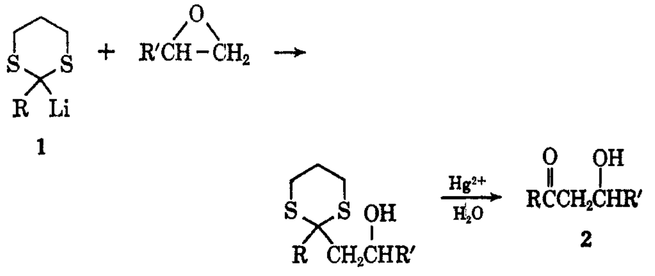
The application of lithio derivatives of 1,3-dithianes to the synthetic modification of 2-cyclohexenone systems has been studied using the parent enone and 2-methyl-1,3-dithiane as models. A variety of synthetically useful structures can be formed by this approach, as is illustrated in the present work by the production of compounds **3**–**8**.

The readily available 2-lithio derivatives of 1,3-dithianes (**1**)[2,3] are valuable intermediates for the construction of organic molecules, since they are synthetically equivalent to C-nucleophilic carbonyl groups. Although the two sulfur substituents provide considerable carbanion stabilization, the lithio reagents of type **1** react readily with most of the functional groups which normally combine with Grignard reagents, *e.g.*, >C=O, >C=N–, –COX, –C≡N, and . The bisthio carbanions derived from dithianes allow the assemblage of polyfunctional systems in ways which are very different from and complementary to traditional synthetic routes. For example, the β-hydroxy ketone system **2**, conventionally obtained by aldol processes, can now be constructed from a different set of carbon groups.



This paper reports the application of 2-lithio-1,3-dithianes, as exemplified by **1**, R = CH_3, to the structural modification of the 2-cyclohexenone system, one of the most important and useful structural types in the synthesis of polycyclic molecules. The major points of interest with conjugated enone systems are (1) the question of 1,2- *vs.* 1,4-addition pathways, (2) the generation of functionality patterns not otherwise accessible, and (3) the possible utilization of the products of addition to generate other useful structures by selective modification of individual functional groups.

The reaction of 2-cyclohexenone with 2-lithio-2-methyl-1,3-dithiane, in fact, follows a 1,2-carbonyl addition course to give the crystalline unsaturated hydroxy derivative **3** in good yield. This structural assignment is supported by the infrared spectrum (OH stretching at 2.80 μ, no carbonyl absorption), the nmr spectrum (2 olefinic H, 5.92 ppm multiplet), and analytical data. The adduct **3** is transformed in high yield to the allylic isomer **4** by treatment with dilute aqueous acid at 25°. Selective oxidation of the secondary alcohol function of **4** in the presence of the dithiane system was readily and efficiently accomplished using active manganese dioxide to give **5**, which could be reduced back to **4** using sodium borohydride. The conjugated ketone **5** was also synthesized directly by the reaction of 2-lithio-2-methyl-1,3-dithiane with 3-isobutoxy-2-cyclohexenone followed by acid hydrolysis.

Selective hydrolysis of the thioketal function in the alcohol **4** and the ketone **5** to give the corresponding carbonyl compounds was readily achieved. In the case of **4** the conversion to the hydroxy ketone **6** was effected under mild conditions using mercuric chloride in aqueous acetonitrile in the presence of cadmium carbonate to remove the acid formed along with the insoluble mercuric mercaptide.[4] The hydrolysis of **5** to give the conjugated enedione **7** was performed using oxidative hydrolysis with N-chlorosuccinimide–silver nitrate combination in aqueous acetonitrile.[4] The enedione **7** was also obtained by oxidation of the unsaturated hydroxy ketone **6** with active manganese dioxide. Reduction of **7** with zinc–acetic acid led to the saturated 1,4-diketone **8**. The hydroxyenone **6** was converted cleanly into the enedione **7** by oxidation with active manganese dioxide and into 1,4-diketone **8** by base-catalyzed rearrangement, demonstrating another route to these substances.

The reactions shown in Scheme I all proceed in good yield under conditions sufficiently mild to be useful with more complex and highly functionalized systems. The synthesis of **6**, **7**, and **8** are particularly illustrative of the potential of the bisthio carbanion reagents for the synthesis of 1,4-dioxygenated structures at a variety of oxidation levels. The analytical and spectral data which follow confirm the structural assignments shown in Scheme I.

Experimental Section

Melting points were determined using a Büchi melting point apparatus and are corrected. Infrared spectra were obtained using a Perkin-Elmer 137 Infracord spectrophotometer and ultraviolet spectra were recorded with a Cary Model 11M recording spectrophotometer. The nmr data were obtained at 60 Mc using a Varian Associates Model A-60 spectrometer and are expressed as shift downfield from internal tetramethylsilane in parts per million. The mass spectra were taken with an Associated Electrical Industries Ltd. Model MS 9 mass spectrometer. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Preparation of 2-Methyl-2-(2-cyclohexen-1-ol)-1,3-dithiane (3) from 2-Methyl-1,3-dithiane and 2-Cyclohexenone.—To a solution of 2-methyl-1,3-dithiane[5] (6.71 g, 0.05 mole), dissolved in dry tetrahydrofuran (150 ml) at −30° under nitrogen, *n*-butyllithium (0.055 mole) was added dropwise.[1,2] After 2 hr

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(1) Undergraduate research student, 1966–1967.

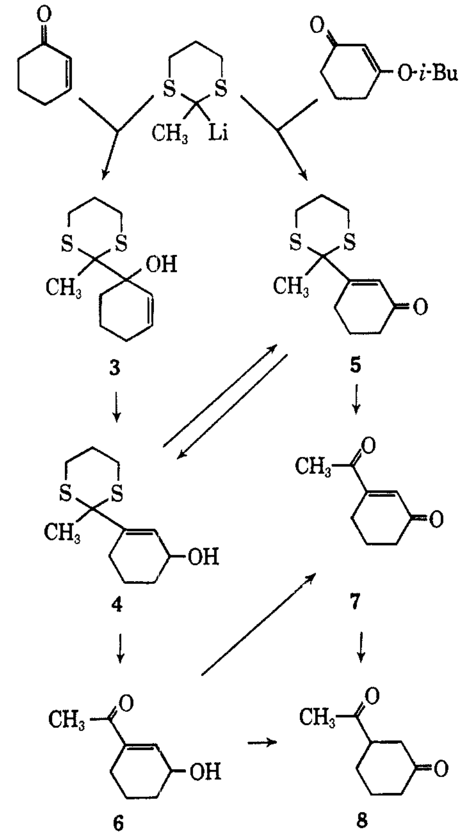
(2) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1075, 1077 (1965).

(3) E. J. Corey, D. Seebach, and R. Freedman, *J. Am. Chem. Soc.*, **89**, 434 (1967).

(4) After a procedure developed by B. W. Erickson in these laboratories.

(5) L. Autenrieth and K. Wolff, *Ber.*, **32**, 1275 (1899).

SCHEME I



at −30°, 2-cyclohexenone (4.80 g, 0.05 mole) was added dropwise. The reaction mixture was stored at 0° for 18 hr, then concentrated under reduced pressure with the rotary evaporator. Water (100 ml) was added to the reaction mixture which was subsequently washed three times with ether. The organic layers were combined, washed five times with water, once with a saturated salt solution, and dried over sodium sulfate. The ether was removed with a rotary evaporator and the product was recrystallized once from an ether–pentane mixture. The oily white crystals were sublimed (0.01 mm, 75°), yielding **3** as a pure product, mp 54.1–55° (7.64 g, 66%). The infrared spectrum (in CCl_4) showed bands at 2.80, 3.40, 7.08, 8.57, 9.41, and 10.38 μ. The nmr spectrum (in CCl_4) showed the two ethylenic protons at 5.92 ppm (2 H, multiplet), the four protons adjacent to the sulfur atoms at 2.63–3.06 ppm (4 H, broad quartet). a broad multiplet at 1.60–2.15 ppm (8 H), and a methyl singlet at 1.58 ppm (3 H).

Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.38; H, 7.88; S, 27.80. Found: C, 57.33; H, 7.94; S, 27.81.

Preparation of 2-Methyl-2-(1-cyclohexen-3-ol)-1,3-dithiane (4) from 2-Methyl-2-(2-cyclohexen-1-ol)-1,3-dithiane (3).—A solution of **3** (3.23 g, 14.0 mmoles) dissolved in dioxane (250 ml) and aqueous 1% sulfuric acid (250 ml) was stirred at room temperature for 5 hr and then extracted three times with ether. The ethereal extracts were combined, washed once with a saturated aqueous sodium bicarbonate solution, three times with water, once with an aqueous sodium chloride solution, and dried (Na_2SO_4). The solvent was removed at room temperature with a rotary evaporator and **4** was obtained as a crude product in 99% yield (3.19 g). The product was a clear, viscous, nondistillable oil which was shown to contain no **3** by tlc and nmr analysis. The molecular weight, determined mass spectrometrically, was 230.0802 (calcd for $C_{11}H_{18}OS_2$, 230.0799). The infrared spectrum (neat) of the product showed broad hydroxyl absorption at 2.93 μ, C=C stretching absorption at 6.08 μ, and characteristic 1,3-dithiane absorption at 11.00 μ. The nmr spectrum (CCl_4) showed peaks at 6.31–6.20 (1 H, multiplet, olefinic), 4.38–4.13 (1 H, adjacent to hydroxyl), 3.77 (1 H, hydroxyl), and 1.54 ppm (3 H, singlet, methyl).

Preparation of 2-Methyl-2-(1-cyclohexen-3-one)-1,3-dithiane (5) from 2-Methyl-2-(1-cyclohexen-3-ol)-1,3-dithiane (4).—A solution of **4** (0.269 g, 1.16 mmoles) in chloroform (11.6 ml) was treated with neutral active manganese dioxide (2.69 g, 48.7 mmoles) prepared according to Henbest, *et al.*[6] The reaction mixture was stirred at room temperature for 3.5 hr, and filtered, and the filtrate was washed twice with chloroform (40 ml each). The chloroform was evaporated at reduced pressure yielding 0.219 g of crude **5** (83%). The nmr and infrared spectra of the crude product showed the absence of **4** and solvent. Three recrystallizations from pentane–benzene (2:1) furnished clear cuboidal crystals: mp 68.4–68.9°; $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 236 mμ (ε 15,500).[7] The infrared spectrum of **5** ($CHCl_3$) showed a carbonyl absorption at 6.00 μ, a C=C stretching absorption at 6.18 μ, and absorption due to 1,3-dithiane at 11.00 μ. The nmr spectrum (CCl_4) showed peaks at 6.38 (1 H, singlet, olefinic), 2.90–1.80 (12 H, multiplet), and 1.57 ppm (3 H, singlet, methyl).

Anal. Calcd for $C_{11}H_{16}OS_2$: C, 57.88; H, 7.07; S, 28.05. Found: C, 57.71; H, 7.05; S, 27.49.

Preparation of 2-Methyl-2-(1-cyclohexen-3-ol)-1,3-dithiane (4) from 2-Methyl-2-(1-cyclohexen-3-one)-1,3-dithiane (5).—A solution of **5** (0.847 g, 3.72 mmoles) and sodium borohydride (3.39 g, 89.5 mmoles) in absolute ethanol (40 ml) was stirred for 30 min at room temperature. The reaction mixture was subsequently diluted with water and extracted with methylene chloride. The organic layer was washed three times with water, once with an aqueous sodium chloride solution, dried (Na_2SO_4), and concentrated, yielding **4** (0.809 g) as a crude oil in 94% yield. The nmr and infrared data showed the crude product to contain no **5** or solvent. The infrared and nmr spectra were identical with those of **4** prepared from 2-methyl-2-(2-cyclohexen-1-ol)-1,3-dithiane.

Preparation of 3-Acetyl-2-cyclohexanol (6) from 4.—A 250-ml three-necked flask was equipped with a water-cooled condenser and a two-way stopcock for maintaining a nitrogen atmosphere. Mercuric chloride (2.81 g, 10.3 mmoles) and freshly prepared cadmium carbonate (1.68 g, 9.8 mmoles) were placed in the flask. A solution of **4** (1.13 g, 4.92 mmoles) in water (2.5 ml) and acetonitrile (47.5 ml) was added under nitrogen to the flask. The reaction mixture was stirred at 50° for 7.5 hr and then concentrated to dryness. The residual powder was washed three times with benzene (50 ml each) and once with chloroform (50 ml). These washings were combined, filtered, and freed of solvent with a rotary evaporator, furnishing 0.554 g of **6** (80%) as a clear oil, bp 135° (0.07 mm). An analytical sample could not be prepared, as distillation was accompanied by decomposition. The nmr spectrum of the crude product showed no trace of starting material or solvent. The molecular weight determined mass spectrometrically was 140.0832 (calcd for $C_8H_{12}O_2$, 140.0837). The infrared spectrum (neat) of **6** showed hydroxyl absorption at 2.90 μ and carbonyl absorption at 6.02 μ. The nmr spectrum (CCl_4) showed peaks at 6.46–6.35 (1 H, multiplet, olefinic), 4.41–3.97 (2 H, hydroxyl and adjacent hydrogen), and 2.14 ppm (3 H, singlet, methyl).

Preparation of 2-Methyl-2-(1-cyclohexen-3-one)-1,3-dithiane (5) from 2-Methyl-1,3-dithiane and 3-Isobutoxy-2-cyclohexenone.—A solution of 2-lithio-2-methyl-1,3-dithiane in 100 ml of tetrahydrofuran was prepared by treating 2-methyl-1,3-dithiane (2.137 g, 16.0 mmoles) with 9.95 ml of *n*-butyllithium (1.6 *M* in *n*-hexane) at −20° for 2.25 hr.[1,2] 3-Isobutoxy-2-cyclohexenone (2.680 g, 16.0 mmoles) was added dropwise to the anion solution at −30°, after which the reaction mixture was kept at 0° for 16 hr. The reaction mixture was diluted with water (30 ml) and the volume then reduced to 50 ml on a rotary evaporator. This solution was then extracted four times with ether. The combined ether extracts were washed five times with water, once with an aqueous sodium chloride solution, and dried (Na_2SO_4). Evaporation of the ether at reduced pressure and recrystallization from 1:1 ether–pentane yielded 2.551 g of **5** (70%) as a pure crystalline product. The melting point (68.1–69.0°) and infrared and nmr spectra were identical with the spectra of **5** obtained from the oxidation of 2-methyl-2-(1-cyclohexen-3-ol)-1,3-dithiane.

Preparation of 3-Acetyl-2-cyclohexenone from 3-Acetyl-2-cyclohexenol (6).—To a solution of **6** (0.108 g, 0.780 mmole) dissolved in chloroform (50 ml) was added neutral manganese dioxide (1.086 g, 12.5 mmoles). The reaction mixture was stirred at room temperature for 2 hr and filtered, and the filtrate

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[6] H. B. Henbest, E. R. H. Jones, and T. C. Owen, *J. Chem. Soc.*, 4909 (1957).

[7] C. Amendolla, G. Rosenkranz, and F. Sondheimer, *ibid.*, 1226 (1954), have reported, for 6β-hydroxyprogesterone, $\lambda_{\max}$ 236 mμ (ε 13,600).

washed once with chloroform (30 ml). The chloroform was evaporated on the rotary evaporator yielding 0.0965 g (90%) of **7** as a crude product. The nmr and infrared spectra showed no trace of starting material in the crude product. Recrystallization from benzene–pentane (1:1) gave **7** as yellow plates: mp 49.9–50.4°; $\lambda_{\max}^{95\%\,\mathrm{EtOH}}$ 245 mμ (ε 13,700).[8] The infrared spectrum of **7** ($CHCl_3$) showed broad carbonyl absorption at 5.85–5.95 μ. The nmr spectrum (CCl_4) of **7** showed peaks at 6.49 (1 H, multiplet, olefinic), 2.41 (3 H, singlet, methyl), and 2.63–1.83 ppm (6 H, multiplet).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.00; H, 7.26.

Preparation of 3-Acetyl-2-cyclohexenone (7) from 2-Methyl-2-(1-cyclohexen-3-one)-1,3-dithiane (5).—A solution of acetonitrile (10 ml), water (4 ml), silver nitrate (0.348 g, 2.05 mmoles), and N-chlorosuccinimide (0.243 g, 1.82 mmoles) was cooled to 0°. A solution of **5** (0.104 g, 0.46 mmole) dissolved in acetonitrile (5 ml) was added dropwise to the stirred reaction mixture followed by a 1-ml acetonitrile rinse. The reaction was carried out under a nitrogen atmosphere and kept at 0° for 25 min. Dimethyl sulfoxide (1 ml) was added after 25 min and the reaction mixture was subsequently warmed to room temperature for 30 min. The reaction mixture was filtered and the filtrate was extracted with chloroform. The organic layer was washed with an aqueous ammonium acetate solution. The aqueous phase was extracted three times with chloroform and the combined chloroform extracts were washed once with water, once with a saturated sodium chloride solution, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator and the residue was put through a 1 × 1.5 cm silica gel column. The column was eluted with 30 ml of benzene which after evaporation yielded **7** (0.0625 g, 100%) as yellow crystals, which were shown to be pure by nmr and tlc analysis. Sublimation at a bath temperature of 45° (0.01 mm) gave pure **7** whose melting point (49.8–50.3°) and infrared and nmr spectra were identical with those of a sample prepared by oxidizing 3-acetyl-2-cyclohexenol.

Preparation of 3-Acetylcyclohexanone (8) from 3-Acetyl-2-cyclohexenol (6).—A solution of **6** (0.463 g, 3.81 mmoles) and potassium hydroxide (0.224 g, 4.0 mmoles) in methanol (30 ml) and water (3 ml) was refluxed in a nitrogen atmosphere. After 14 hr, 50 ml of water was added to the reaction mixture and this solution was extracted three times with chloroform (50 ml each). The combined chloroform extracts were washed once with an aqueous sodium bicarbonate solution, twice with water, once with an aqueous sodium chloride solution, and dried (Na_2SO_4). The solvent was removed with a rotary evaporator yielding **8** (0.450 g, 97% yield) as a clear crude oil, bp 79–81° (0.02 mm) (lit.[9] bp 140–145°, (15 mm)). Nmr and tlc analysis of the crude product showed the absence of **6**. After distillation the oil crystallized on standing, mp 37.4–38.3° (lit.[9] mp 39°). The molecular weight determined mass spectrometrically was 140.0837 (calcd for $C_8H_{12}O_2$, 140.0837). The infrared spectrum (neat) of **9** showed a broad carbonyl absorption at 5.8–5.9 μ. The nmr spectrum (CCl_4) exhibited peaks at 3.03–2.53 (1 H, multiplet), 2.14 (3 H, singlet, methyl), and 2.42–1.45 ppm (8 H, multiplet).

Preparation of 3-Acetylcyclohexanone (8) from 3-Acetyl-2-cyclohexenone (7).—Compound **7** (0.099 g, 0.718 mmole) was dissolved in acetic acid (10 ml) and water (3 ml) and stirred at room temperature in the presence of powdered zinc (0.510 g, 7.81 mmoles). After 4.5 hr the reaction mixture was filtered, diluted with water (50 ml), and extracted four times with chloroform. The combined chloroform extracts were washed twice with an aqueous sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed with a rotary evaporator yielding **8** (0.098 g, 98% yield) as a crude product. The melting point (37.2–38.3°) and infrared and nmr spectra were identical with those of **8** obtained under basic conditions from 3-acetyl-2-cyclohexenol. The crude product contained no **7** or solvent by nmr and tlc analysis.

Registry No.—**3**, 15040-92-3; **4**, 15040-93-4; **5**, 15040-94-5; **6**, 15040-95-6; **7**, 15040-96-7; **8**, 15040-97-8.

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(8) C. Amendolla, G. Rosenkranz, and F. Sondheimer,[7] have reported, for cholest-4-ene-3:6-dione, $\lambda_{\max}$ 250 mμ (ε 11,200).

(9) A. McCoubrey, *J. Chem. Soc.*, 2931 (1951).

A New Synthetic Route to Cyclic Mono- and Diketone Derivatives *via* Bisthio Carbanions

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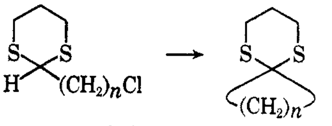
The synthesis of a series of 1,3-propylene thioketal derivatives of cyclic ketones having three, four, five, six, and seven ring members is described to illustrate a new method for ring formation which depends on an intramolecular displacement reaction of 2-haloalkyl-1,3-dithianes.

The 2-lithio derivatives of 1,3-dithianes react readily with halides to afford 2-alkylated dithianes in excellent yield.[2a] This paper reports the successful development of the intramolecular analog of this process which provides a new and useful route to a wide range of cyclic mono- and diketones.[2b,c]

In its simplest form the cyclization is illustrated by the conversion of the 2-(ω-chloroalkyl)-1,3-dithianes **1a–e** into the cycloalkanone trimethylenethioketals **2a–e** (see eq 1). The ring closure has been effected simply by treatment of the chloroalkyldithianes **1** in tetrahydrofuran under nitrogen at −70° to 0° with an equivalent of *n*-butyllithium reagent in hexane. Ring formation proceeded efficiently at normal preparative concentration with uniformly good yields (*ca.* 80%) being obtained in the case of the three, four, five, and six-membered rings. The yield of cyclization product **2e** having a seven-membered ring was somewhat less, 67%. Preliminary studies indicate that the efficiency of cyclization to form an eight-membered ring is very



1a–e, $n = 2–6$ **2a–e**, $n = 2–6$ (1)

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(1) Undergraduate research student, 1966.

(2) (a) E. J. Corey and D. Seebach, *Angew. Chem. Intern. Ed. Engl.*, **4**, 1075, 1077 (1965). (b) For a preliminary presentation of part of this work, see E. J. Corey, *Pure and Appl. Chem.*, **14**, 19 (1967). (c) Application of 2-lithio-1,3-dithianes to other synthetic problems has been described: E. J. Corey, D. Seebach, and R. Freedman, *J. Am. Chem. Soc.*, **89**, 434 (1967); E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).