HYDROLYSIS OF KETOL TRIMETHYLENEDITHIOACETALS. ATTEMPTED SYNTHESIS OF YASHABUSHIKETOL+

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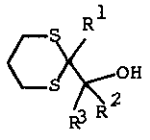
Abstract- Thallium(III) trifluoroacetate has been shown to cleave dithianes which contain hydroxy functions that other reagents fail. Hydrolysis of a direct precursor of yashabushiketol led to tetrahydro-γ-pyrones, however.

Many methods for dethioacetalization[1] have been developed indirectly as a result of exploiting reactivity umpolung based on dithiane chemistry. However, most of these procedures were applied to rather simple molecules. In 1972, Jones and Grayshen [2] reported a complete failure of hydrolyzing certain steroidal dithianes with the mercury(II) chloride-cadmium carbonate system Later, Carlson et al.[3] encountered serious difficulties during deblocking of dihydro-γ-pyrone and furanone dithianes. Thus, it appears that the presence of a hydroxyl function is unfavorable to the otherwise straightforward reaction.

We felt thallium(III) trifluoroacetate [4] could be used to hydrolyze ketol dithioacetals advantageously, in view of the fast reaction rates and the apparent stability of the alcohol group toward thallium(III) species. Accordingly, several dithiane derivatives **1** were prepared and submitted to the oxidative cleavage. α-Ketols (**2**) have been recovered in good yields (see Table 1). However, it should be noted that these reations are relatively slow as compared to those of simple dithioacetals, and in some cases two equivalents of the reagent are needed. It is noted also that benzene rings are not attacked under such conditions although thallation is a facile process.

+TLH wishes to dedicate this paper to Professor E.J. Corey on the occasion of his 60th birthday.

To further test the scope of this reaction we engaged in a synthesis of yashabushiketol (**3**) which incorporates dethioacetalization of a β-ketol derivative as the final step. Yashabushiketol is a C_6-C_7-C_6 natural product isolated from the male flower of *Alnus firma* Sieb., and its structure was elucidated by Asakawa.[5] The dihydro derivative of yashabushiketol has been synthesized from condensation of a 2,4-pentanedione borate complex with benzaldehyde, followed by hydrogenation. This approach evidently cannot be modified to gain entry into **3** because of the the lack of control in the reduction step.



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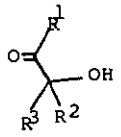

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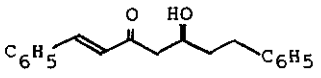


3

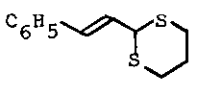
a R^1=CH_3, R^2+R^3=$(CH_2)_5$

b R^1=R^2=C_6H_5, R^3=H

c R^1=H, R^2+R^3=$(CH_2)_4$

d R^1=H, R^2=R^3=C_6H_5

Condensation of cinnamaldehyde with 1,3-propanedithiol under standard conditions furnished the dithiane **4** in 85% yield. Addition of *n*-butyllithium to a tetrahydrofuran solution of **4** resulted in rapid deprotonation of the latter compound to give a deep red anion which was reacted with epoxide **5**. The product has the desired structure **6** as indicated by ^{1}H nmr [vinylic hydrogens as a pair of doublets at δ 6.85 and 7.22 (J=16 Hz)]. Unfortunately, attempts to generate yashabushiketol from **6** were unsuccessful. Protection of the hydroxyl group in the form of acetate, trifluoroacetate, and trimethylsilyl ether did not improve the situation. Under all experimental conditions we tried a diastereomeric mixture of two tetrahydro- γ-pyrones was obtained (Table 2). More significantly, trifluoroacetic acid alone is capable also to induce a partial hydrolysis (an equilibrium between the starting material and the product seemed to have been set up after 2 h at room temperature), while ordinary dithianes such as the 2-phenyl derivative are completely stable.



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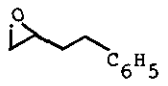

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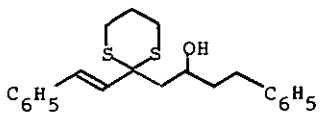

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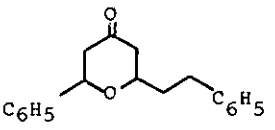
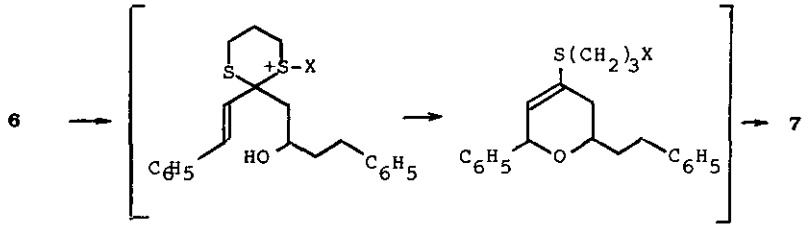


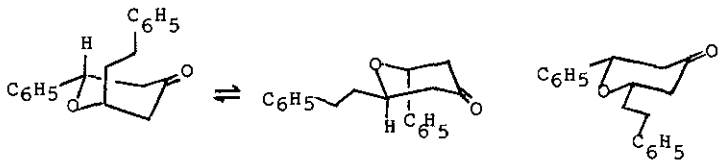
7

A plausible mechanism for the reaction is shown in Scheme 1. The facile scission of the C-S bond must be due to the formation of a stable tertiary carbocation which is flanked by a styryl and a sulfenyl group. Ring formation with hydroxyl participation follows logically. Alternatively, the reaction pathway may involve oxidative cleavage to generate the hydroxy enone which then undergoes the cyclization.

Scheme 1.



Tentative stereochemical assignment of the two isomers of **7** was based principally on spectral grounds. Isomer **A** absorbs in the infrared at 1725 cm^{-1} ,whereas isomer **B** displays a carbonyl band at 1720cm^{-1}. In the ^{1}H-nmr spectra, isomer **A** shows a pseudo singlet for the aromatic protons at δ 7.10, a broad unresolved signal centred at δ 4.25 which is ascribed to the benzyl ether methine proton (H-2), and the rest of the spectrum consists of two rather symmetrical bands of equal intensity [δ 2.4-3.0, 1.6-2.1] and a multiplet at δ 3.20 for the other ethereal proton. On the other hand, isomer **B** exhibits two singlets at δ 7.23 and 7.08 (ArH) a quartet at δ 4.45 (J=9.5 , 4.5 Hz) due to H-2 which must be axially oriented, a multiplet at δ 3.55 for H-6, and multiplets of relatively sharp signals between δ 1.5 and 2.9 .



7A **7B**

Assuming that chair conformations prevail in these molecules, the ^{1}H-nmr data strongly suggest that **A** is the trans isomer existing in a dynamic equilibrium, and **B** has a cis stereochemistry. The assignments are supported by the higher frequency absorption of the ketonic band of isomer **A** in the infrared, due to a ubiquitous axial substituent in **A**. By virtue of a reflex effect[6] which exerts a pinching of the internal bond angle of the carbonyl group the C=O stretching appears at a higher frequency.

Table 1. *TTFA Cleavage of α-Ketol Dithioacetals*

Dithianes	TTFA (equiv)	Reaction Time (h)	α-Ketol ,Yield (%)
1a	1	0.5	**2a** (70)
1b	1	0.5	**2b** (77)
1c	2	1	**2c** (75)
1d	2	2	**2d** (79)

Table 2. Hydrolysis of **6** to

Reagents	Yield, %	
	7A	**7B**
$Tl(OCOCF_3)_3$	23	30
$CuCl_2$-CF_3COOH	28	37
HgO-HF_3-OEt_2	35.5	10
$HgCl_2$-$NaHCO_3$	21	28
CH_3I	24	29

EXPERIMENTAL

Benzoin propylenethioacetal **(1b).**

To a stirred solution of 2-phenyl-1,3-dithiane (980 mg, 5 mmol) in dry tetrahydrofuran (15 ml) which had been placed under nitrogen and cooled to -30° C was added *n*-butyl lithium (2.3*M* in hexane, 2.18 ml, 5mmol) via a syringe. After 1h, benzaldehyde (636 mg, 6 mmol) was added, and the reaction mixture was left at -10°to -5°C for 2.5 h., when it was quenched with aq. ammonium chloride and extracted with chloroform (3x30 ml). Evaporation of the dried extracts yielded a white solid which was recrystallized from methanol to give **1b** (1.23 g, 81.5%), mp 130.5-131.5 °C; Ir (CH_2Cl_2) ν 3620, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.6–2.2 (2H, m), 2.5–2.8 (5H, m), 4.97 (1H, s), 6.7–7.4 (8H, m), 7.5–7.8 (2H, m) .

Anal. Calcd for $C_{17}H_{18}OS_2$: C, 67.51; H, 6.00. Found: C, 67.53; H, 6.03.

2-Phenyl-2-hydroxycyclopentyl-1,3-dithiane **(1c).**

The reaction of 2-phenyl-1,3-dithiane (5 mmol) with cyclopentanone (5.5 mmol), carried out in the same manner as the above example, gave, after distillation at 140°C(0.2 torr) and recrystallization of the solidified distillate from ether-petroleum ether, **1c** (1.28 g, 91.5%), mp 84-85.5° C. Ir (CH_2Cl_2) ν 3600, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ1.2-2.4 (11H, m), 2.5-2.8 (4H, m), 7.2-7.6 (3H, m), 7.9-8.2 (2H, m).

Anal. Calcd for $C_{15}H_{20}OS_2$: C, 64.24; H, 7.19. Found: C, 64.30; H, 7.15.

2-Methyl-2-hydroxycyclohexyl-1,3-dithiane **(1a).**

Obtained in 83% yield by the standard procedure, bp 125-130° C (0.2 torr) [lit.[7] b.p. 165° C (1.2 torr)].

2-Diphenylhydroxymethyl-1,3-dithiane **(1d).**

Prepared in 77% yield, mp 136-137°C [lit.[7] mp 136-136.5°C].

General Procedure for TTFA Hydrolysis of α-Ketol Dithioacetals.

Following the method of Ho and Wong,[4] the hydrolysis was performed at room temperature under conditions specified in Table 1. The product was extracted with chloroform, purified by preparative tlc on silica gel, and identified with an authentic sample.

2-Styryl-1,3-dithiane **(4).**

A mixture of cinnamaldehyde (3.3 g, 25 mmol), 1,3-propanedithiol (2.97 g, 27 5 mmol), and boron trifluoride etherate (1.5 ml) in chloroform (125 ml) was stirred at room temperature for 15 h. It was washed with 2*N* sodium hydroxide, water, and dried with magnesium sulfate. Distillation of the organic extracts furnished **4** (4.695 g, 85%), bp145-150° C (0.2 torr) as a thick oil which solidified on standing. After recrystallization from methanol the product melted at 57.5-58° C. Ir (CH_2Cl_2) ν1678, 1642, 1600, 1568 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1 6-2.2 (2H, m), 2.7-3.0 (4H, m), 4.75 (1H, d, J=7 Hz), 6.23 (1H, q, J=16, 7Hz), 6.77 (1H, d, J=16 Hz), 7.28 (5H, br. s). Anal. Calcd for $C_{12}H_{14}S_2$: C, 64.84; H, 6.35. Found C, 64 89; H, 6.30.

Dithiane **6.**

The deep red lithiodithiane solution generated from **4** (1.22 g, 5.5 mmol) with *n*-butyllithium (2.3*M*, 2.6 ml, 5.9 mmol) in anhydrous tetrahydrofuran (15 ml) under nitrogen at -30° to -20°C during 0.5 h. Introduction of epoxide **5** (888 mg, 6.0 mmol) to the stirred anion solution discharged the color immediately. After another 40 min the reaction mixture was quenched with aq. ammonium chloride. A thick oil was obtained after chloroform extraction work up and this was purified by preparative tlc on silica gel to give **6** (1.823 g, 89.5%). Attempted distillation led to partial decomposition. Ir (CH_2Cl_2) ν 3630, 3520, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ1.5-2.3 (6H, m), 2 4-3.2 (7H, m), 4.05 (1H, m), 6.22 (1H, d, J=16 Hz), 6.85 (1H, d, J=16 Hz), 7 13 (5H, s), 7.3-7.5 (5H, m); MS (70 ev) m/z 370 ($M^{+\cdot}$).

Hydrolysis of **6** *with Cupric Chloride-Trifluoroacetic Acid.*

Dithiane **6** (481 mg, 1.03 mmol) was dissolved in chloroform (8 ml) and treated with cupric chloride dihydrate (375 mg), trifluoroacetic acid (0.5 ml) and one drop of water for 16 h at room temperature. The reaction mixture was filtered and the filtrate diluted with choroform and washed with water. The crude product obtained from the chloroform extract was chromatographed on preparative silica gel plates using 1:1 benzene-chloroform as eluent ; two compounds were isolated.

7A (100 mg, 28%; R_f 0.31). Ir (CH_2Cl_2) ν1725, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ1.6-2.1 (4H, m), 2.4-3.0 (4H, m), 3.20 (1H, m), 4.25 (1H, m), 7.10 (10H, s).. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found C, 81.19; H 7.28

7B (135 mg, 37%; R_f 0.55). Ir (CH_2Cl_2) ν1720, 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ1.5-2.9 (8H, m), 3.55 (1H, m), 4.45 (1H, q, J=9.5, 4.5Hz), 7.08 (5H, s), 7.23 (5H, s). Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.32, H, 7.25.

[The experimental portion is taken from part of the M.Sc. Thesis submitted by RJH to the Department of Chemistry, University of Manitoba in 1973.]

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