Pergamon

Tetrahedron, Vol. 52, No. 13, pp. 4679-4686, 1996
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0040-4020/96 $15.00 + 0.00

S0040-4020(96)00139-1

Stepwise Controlled Reduction of α-Oxoketene Dithioacetals with Zn/$ZnCl_2$-TMEDA in Ethanol

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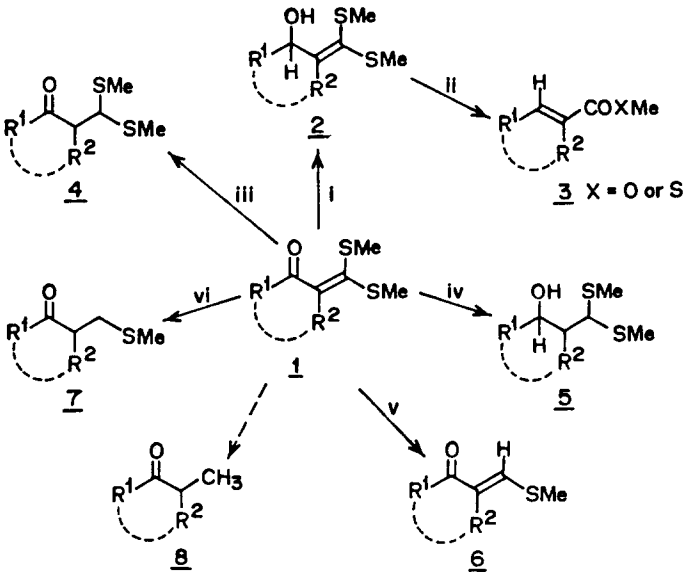
Abstract: α-Oxoketene dithioacetals **1** are shown to undergo highly selective conjugate reduction with Zn/$ZnCl_2$-TMEDA in refluxing ethanol under controlled reaction conditions to afford ß-methylthiomethylene ketones **6**, ß-methylthioketones **7** and the completely desulphurized α-methylketones **8** in sequential manner.

Regioselective reduction of αß-unsaturated carbonyl compounds is an important synthetic transformation in organic chemistry.[1] Particularly, the related systems with ß-heteroatoms functionalities further add to synthetic challenges as they significantly influence the differential electrophilicity of all the three carbon atoms.[2,3] The α-oxoketene dithioacetals with two alkylthio groups at ß-position of the enone serve as excellent models for regio-, stereo- and chemoselective reduction and C-C bond formation reactions,[4] besides, the resulting reduced functionalities are usuful intermediates for further synthetic transformations.[4,5] Several studies on regiospecific reduction of α-oxoketene dithioacetals with various reducing agents have been reported in the literature (Scheme 1). Thus 1,2- and 1,2,3,4-reductions are mostly achieved with nucleophilic metal hydride ($NaBH_4$[5c-e] and $LiAlH_4$[5b]) and the resulting carbinols (**2** and **5**) with latent ester (or aldehyde) functionalities are useful substrates for 1,3-carbonyl transpositions affording αß-unsaturated polyene esters or aldehydes respectively.[5c-e] Of particular importance are conjugate 1,4 reduction[4,6] of α-oxoketene dithioacetals, since the products in these reactions are ß-functionalized carbonyl compounds in which the oxidation level of α- and ß-carbon can be adjusted by the choice of the reducing agents. Thus sodium borohydride (in acetic acid),[6b] magnesium (in methanol),[6c] and DIBAL.TEA[6a] reduction afford ß-oxodithioacetals **4** which are shown to be useful precursors for aromatic annelation[7a] and enealdehydes synthesis.[7b] In our laboratory, we have further demonstrated selective dethiomethylation of **1** with either $NiCl_2/NaBH_4$[8] or $NaCNBH_3$[6b] yielding ß-alkylthioenones **6** (Scheme 1). However yields of **6** were inconsistant particularly for aliphatic ß-alkylthioenones which are used as intermediates for the synthesis of both natural and unnatural polyenes with terminal aldehyde functionality.[9] Finally, the reduction of **1** with weaker electrophilic reagents like 9-BBN[6a] or catecholborane[6a] affords ß-alkylthio ketones **7** (or mixture of **7**



i. $NaBH_4$ /MeOH ii. $BF_3.Et_2O$/MeOH or $BF_3.Et_2O/H_2O$ iii. $NaBH_4$ /AcOH or DIBAL iv. $LiAlH_4$ /THF v. $NiCl_2$ /$NaBH_4$ or $NaBH_3CN$ vi. 9-BBN

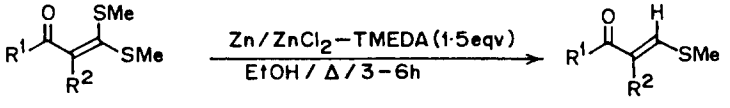
Scheme 1

and **4**) in which reductive dethiomethylation is accompanied with concurrent reduction of double bond also. As part of our programme to explore the chemistry of α-oxoketene dithioacetals, we were interested in developing a mild reducing system capable of controlling the oxidation levels at the ß-carbon of α-oxoketene dithioacetals in a sequential manner by manipulation of the reaction conditions and the stoichiometry of the reagent. In particular, we were interested in an efficient high yield method for conversion of **1** to ß-alkylthioenones **6**, in view of their utility in organic synthesis.[9] We now report in this paper an efficient reagent system involving Zn/$ZnCl_2$-TMEDA complex for the reduction of **1** in a controlled manner. Depending on the stoichiometry of the reagent and the reaction time, **1** undergoes reduction at various stages to afford exclusively either **6** in high yields or **7** and **8** in moderate yields.

RESULTS AND DISCUSSION

Reduction of **1** with Zn/$ZnCl_2$ in ethanol (Dekker's procedure[10]) was first investigated. Thus a suspension of **1a**, Zn (3 eqv.) and $ZnCl_2$ (1.5 eqv.) in ethanol was stirred at room temperature (7 hr) followed by work up of the reaction mixture to afford **6a** in 85% yield. However the yield of **6a** was not

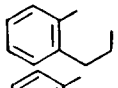
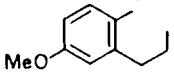
consistent due to the hygroscopic nature of $ZnCl_2$, besides, the subsequent reduction of **1** did not show any selectivity for their conversion to either **7** or **8** under controlled conditions. We have found that clear reduction of **1a** to ß-methylthioenone **6a** could be achieved in consistently high yields by using Zn (3 eqv.) and $ZnCl_2$-TMEDA complex[11] (1.5 eqv.) in refluxing ethanol (4hr). The yields of **6a** were identical in all repeat experiments. Scheme 2 displays some of the results obtained for the reduction of few selected α-oxoketene dithioacetals from aromatic and aliphatic acyclic and cyclic ketones. Especially, the reduction of α-acetylketene dithioacetal **1d** from acetone is particularly important, since the corresponding S-(*t*-butyl) analog of the resulting ß-methylthioenone **6d** is a useful intermediate in the synthesis of polyenealdehydes.[9] Similarly the other aliphatic (**1e-f**) and cyclic (**1g-i** and **1j-k**) ketene dithioacetals yielded the corresponding ß-methylthioenones **6e-k** in 75-95% overall yields.[12]The products



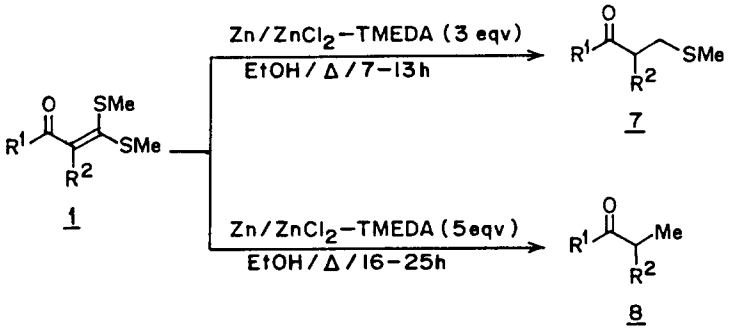
1 6

Scheme 2

Table 1: Selective Reduction of α-Oxoketene Dithioacetals **1a-k** to ß-Methylthioenones **6a-k**.

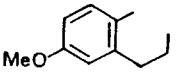
Entry	1	6	R^1	R^2	% Yield **6** (Time hr)
1	**1a**	**6a**	C_6H_5	H	85 (4)
2	**1b**	**6b**	C_6H_5	CH_3	80 (3)
3	**1c**	**6c**		H	60 (2)
4	**1d**	**6d**	CH_3	H	95 (7)
5	**1e**	**6e**	CH_3	CH_3	95 (3)
6	**1f**	**6f**	CH_3	C_2H_5	95 (3)
7	**1g**	**6g**	$-(CH_2)_3-$		75 (3)
8	**1h**	**6h**	$-(CH_2)_4-$		95 (3)
9	**1i**	**6i**	$-(CH_2)_6-$		92 (3)
10	**1j**	**6j**			90 (3)
11	**1k**	**6k**			90 (3)

of overreduction were not detected. In an another experiment, when **1a** was treated with 3 eqv. of $Zn/ZnCl_2$-TMEDA complex and the reaction mixture was refluxed for 8 hr (monitored by tlc), the corresponding ß-methylthio ketone **7a** was obtained in 65% yield. Similarly the other dithioacetals (**1b-e**, **1h** and **1k**) yielded the respective ß-methylthio ketones **7b-e**, **7h** and **7k** in moderate to good yields under controlled conditions (Scheme 3). Finally, treatment of **1a** with 5 eqv.of the reagent under identical reaction conditions for prolonged time (18 hr) resulted in complete reductive desulphurization of both the methylthio groups to afford the corresponding α-methylketone (propiophenone) **8a** in 55% yield (Scheme 3). Similarly the other representative ketene dithioacetals **1b-e**, **1h** and **1k** could also be converted to the corresponding fully desulphurized α-methylketones **8b-e** and **8h** and **8k** in 50-85 % overall yields under similar reaction conditions.



Scheme 3

Table 2: Reduction of α-Oxoketene Dithioacetals **1** to ß-Methylthioketones **7** and α-Methylketones **8**.

Entry	1	R^1	R^2	% Yield 7 (Time hr)	% Yield 8 (Time hr)
1	**1a**	C_6H_5	H	65 (8)	55 (18)
2	**1b**	C_6H_5	CH_3	68 (7)	82 (16)
3	**1c**		H	65 (7)	50 (20)
4	**1d**	CH_3	H	55 (7)	53 (17)
5	**1e**	CH_3	CH_3	73 (12)	65 (25)
6	**1h**	$-(CH_2)_4-$		55 (8)	59 (22)
7	**1k**			70 (7)	85 (16)

In summary, we have demonstrated the potentiality of $Zn/ZnCl_2$-TMEDA system for selective reduction of α-oxoketene dithioacetals to more important ß-methylenones in high yields. The methodology is also applicable with equal efficiency for the preparation of **7** and **8** with full control on product distribution. Several routes for the synthesis of ß-alkylthioenones **6** have been reported in the literature.[9,13] The most commmonly employed methods involve the treatment of α-formylketones (or their tosyl derivatives) with butyl mercaptan.[9a-b,13a] The other methods involve either 1,4-addition of alkyl/aryl mercaptans to ß-ketoacetylene[9c-d,13b-c] or the displacement reaction on ß-chlorovinyl ketones with appropriate mercaptans.[9d,13d] The present method constitutes a simple and cheap high yield alternative for these class of compounds from α-oxoketene dithioacetals.

EXPERIMENTAL

Melting points were determined on a "Thomas Hoover" capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in $CDCl_3$ or CCl_4 using TMS as internal standard and chemical shifts are expressed in δ (ppm) units downfield from TMS. The coupling constants are given in Hertz (Hz). Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer.

Commercially available zinc dust (AR grade, Merck), $ZnCl_2$ (Merck), TMEDA (Merck), and ethanol were used for reactions. Zn dust was activated with 1,2-dibromoethane and $ZnCl_2$ was fused and powdered prior to use. The $ZnCl_2$-TMEDA complex was made according to the reported procedure.[11a] Thin-layer chromatography was performed on glass plates coated with Acme's silica gel containing 13% calcium sulphate as binder and the spots were detected in iodine chamber or by spraying the plates with a solution of acidic $KMnO_4$. Acme's silica gel (60-120 mesh) was used for column chromatography.

All the α-oxoketene dithioacetals required for the present investigation were prepared according to the earlier reported procedures.[14]

General Procedure for the Reduction of α-Oxoketene Dithioacetals with $Zn/ZnCl_2$-TMEDA in Ethanol.

To a well stirred solution of α-oxoketene dithioacetals **1** (10 mmol) in ethanol (25 mL), Zn dust (30 mmol) and $ZnCl_2$-TMEDA complex (15 mmol in the case of **6**, 30 mmol in the case of **7** and 50 mmol in the case of **8**) were added. The reaction mixture was refluxed for 3-25 hr (monitored by t.l.c.) (Table), cooled and the inorganic material was filtered off. The filtrate was poured over crushed ice, treated with 5% sulphuric acid and extracted with chloroform (3 x 50 ml). The combined organic extracts was washed with water (2 x 100 ml), dried over sodium sulphate and concentrated to give the viscous residues, which on column chromatography over silica gel using hexane:ethyl acetate (47:3) as eluent gave the corresponding products **6**, **7** and **8**.

The following known compounds were characterized by comparison of their IR and NMR spectal data with those reported in the literature **(6a)**,**(6d)**,**(6g)**,**(6h)**,[8] **(6b)**,**(6e)**,**(6k)**,[6b] **(8a)**,**(8b)**,[15a] **(8c)**,[15b]

(8d),[15c] **(8e)**,[15d] **(8h)**,[15e] and **(8j)**[16]. The spectral and analytical data of the unknown compounds are given below.

E-3-Methylthio-1-(2-furyl)-2-propen-1-one (6c). Viscous oil; IR (CCl_4) 1645, 1625 cm^{-1}; ^1H NMR (CCl_4) δ 2.42 (s, 3H, SC*H*$_3$), 6.52 (m, 1H, *furyl*), 6.73 (d, 1H, J=16, *olefinic*), 7.21 (m, 1H, *furyl*), 7.61 (brs, 1H, *furyl*), 7.98 (d, 1H, J=16, *olefinic*). [Anal. calcd. for $C_8H_8O_2S$ (168.21): C, 57.12; H, 4.79%. Found C, 57.31; H, 4.74%].

E-4-Methylthio-3-ethyl-3-buten-2-one (6f). Viscous oil; IR (CCl_4) 1674 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (t, 3H, J=6, CH_2CH_3), 2.20 (s, 3H, SC*H*$_3$), 2.26 (q, 2H, J=6, CH_2CH_3), 2.45 (s, 3H, CH_3), 7.32 (s, 1H, *olefinic*). [Anal. calcd. for $C_7H_{12}OS$ (144.23): C, 58.29; H, 8.39%. Found C, 58.15; H, 8.42%].

E-2-(Methylthiomethylene)cyclooctanone (6i). Yellow crystalline solid; m.p. 40-41°C; IR (CCl_4) 1715, 1660,cm^{-1}; ^1H NMR (CCl_4) δ 1.43-1.90 (m, 8H), 2.50 (s, 3H, SC*H*$_3$), 2.43-2.77 (m, 4H), 7.40 (s, 1H, *olefinic*). [Anal. calcd. for $C_{10}H_{16}OS$ (184.30): C, 65.17; H, 8.75%. Found: C, 65.32; H, 8.72%].

3-Methylthio-1-phenylpropan-1-one (7a). Viscous oil; IR (CCl_4) 1706 cm^{-1}; ^1H NMR (CCl_4) δ 2.03 (s, 3H, SC*H*$_3$), 2.63-3.30 [m, 4H, (CH_2)$_2$], 7.28-7.63 (m, 3H, Ar*H*), 7.82-8.18 (m, 2H, Ar*H*). [Anal. calcd. for $C_{10}H_{12}OS$ (180.26): C, 66.63; H, 6.71%. Found C, 66.72, H, 6.68%].

3-Methylthio-2-methyl-1-phenylpropan-1-one (7b). Viscous oil; IR (CCl_4) 1685 cm^{-1}; ^1H NMR (CCl_4) δ 1.26 (d, 3H, J=7, CH_3), 2.03 (s, 3H, SC*H*$_3$), 2.50 (dd, 1H, J=15, 6.5, CH_2), 2.90 (dd, 1H, J=15, 6.5, CH_2), 3.41-3.80 (m, 1H, C*H*), 7.32-7.68 (m, 3H, Ar*H*), 7.85-8.13 (m, 2H, Ar*H*). [Anal. calcd. for $C_{11}H_{14}OS$ (194.29): C, 68.00; H, 7.26%. Found C, 67.89, H, 7.30%].

3-Methylthio-1-(2-furyl)propan-1-one (7c). Viscous oil; IR (CCl_4) 1714 cm^{-1}; ^1H NMR (CCl_4) δ 2.12 (s, 3H, SC*H*$_3$), 2.51-3.10 [m, 4H, (CH_2)$_2$], 6.48 (m, 1H, *furyl*), 7.09 (m, 1H, *furyl*), 7.58 (brs, 1H, *furyl*). [Anal. calcd. for $C_8H_{10}O_2S$ (170.23): C, 56.45; H, 5.92%. Found C, 56.18; H, 5.97%].

4-Methylthiobutan-2-one (7d). Viscous oil; IR (CCl_4) 1730, cm^{-1}; ^1H NMR (CCl_4) δ 2.02 (s, 3H, CH_3), 2.11 (s, 3H, SC*H*$_3$), 2.67 [brs, 4H, (CH_2)$_2$]. [Anal. calcd. for $C_5H_{10}OS$ (118.19): C, 50.81; H, 8.53%. Found C, 50.87; H, 8.58%].

4-Methylthio-3-methylbutan-2-one (7e). Viscous oil; IR (CCl_4) 1713 cm^{-1}; 1H NMR (CCl_4) δ 1.15 (d, 3H, J=7, CH_3), 2.08 (s, 3H, CH_3), 2.16 (s, 3H, SC*H*$_3$), 2.33-2.64 (m, 1H, C*H*), 2.66-2.92 (m, 2H, CH_2). [Anal. calcd. for $C_6H_{12}OS$ (132.22): C, 54.50; H, 9.15%. Found C, 54.38; H, 9.18%].

2-Methylthiomethylcyclohexanone (7h). Viscous oil; IR (CCl_4) 1707 cm^{-1}; ^1H NMR (CCl_4) δ 2.01 (s, 3H, SC*H*$_3$), 1.31-2.91 (m, 11H, CH_2, C*H*). [Anal. calcd. for $C_8H_{14}OS$ (158.26): C, 60.72; H, 8.92%. Found C, 60.94; H, 8.86%].

2-Methylthiomethyl-6-methoxy-1-tetralone (7k). Viscous oil; IR (CCl_4) 1674, 1599 cm^{-1}; ^1H NMR (CCl_4)

δ 2.35 (s, 3H, SCH_3), 2.48-3.22 (m, 7H, CH_2, CH), 3.70 (s, 3H, OCH_3), 6.65-6.93 (m, 2H, ArH), 7.82 (d, 1H, J=8.5, ArH). [Anal. calcd. for $C_{13}H_{16}O_2S$ (236.33): C, 66.07; H, 6.82%. Found C, 66.14; H, 6.80%].

Acknowledgement: KMY and JRS thank CSIR, New Delhi for Senior Research Fellowship and Junior Research Fellowship respectively. Financial assistance under CSIR research scheme is also acknowledged.

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(*Received in UK* 13 *November* 1995; *revised* 29 *January* 1996; *accepted* 1 *February* 1996)