Reactions of α-Hydroxyketene Dithioacetals with Lawesson's Reagent: An Efficient Method for the Synthesis of α,β-Unsaturated Dithioesters

Satheesh K. Nair, Ann Maria Jose, C. V. Asokan*

School of Chemical Sciences, Mahatma Gandhi University, Priyadarshini Hills P. O., Kottayam, 686 560, India
E-mail: asokancv@yahoo.com

Received 10 March 2004; revised 20 January 2005

Abstract: The α-hydroxyketene dithioacetals **2** and **5**, obtained from α-oxoketene dithioacetals by the 1,2-reduction or the 1,2-addition of carbon nucleophiles, on treatment with Lawesson's reagent afforded α,β-unsaturated dithioesters **3** and **6** in good yields.

Key words: ketene dithioacetals, dithiocarboxylates, Lawesson's reagent, thionation, heterodienes

Synthetic methods for α,β-unsaturated dithioesters have received considerable interest in view of their increased reactivity, compared to their carboxylic analogues, as potential dienes or dienophiles in hetero Diels–Alder cycloadditions.[1] Moreover, the cycloaddition products, dihydrothiopyrans, are potential precursors of a wide range of thioheterocycles with interesting biological properties.[2] A recent report describes the synthesis of phosphono-substituted dihydrothiopyrans using α-phosphono-α,β-unsaturated dithioesters.[3] There are very few general methods available for the synthesis of α,β-unsaturated dithioesters and those known are mostly specific to certain substrate classes. The methods available in the literature include (i) alkylation of thiolate anions obtained by the addition of vinyl cuprates to carbon disulfide;[4] (ii) isomerization of γ,δ-unsaturated dithioesters;[5] (iii) base-catalyzed elimination of β-hydroxy dithioesters;[6] and (iv) Wittig–Horner, Peterson or Mukaiyama type condensation reactions of aldehydes and ketones.[7] Hartke et al. have also shown that α,β-unsaturated amides can be transformed into the corresponding dithioesters by a sequence of reactions involving thionation, alkylation and sulfhydrolysis.[8] As part of our studies on the sulfhydrolysis of α-oxoketene dithioacetals we have uncovered a general method for the preparation of substituted α,β-unsaturated dithioesters starting from readily available intermediates.

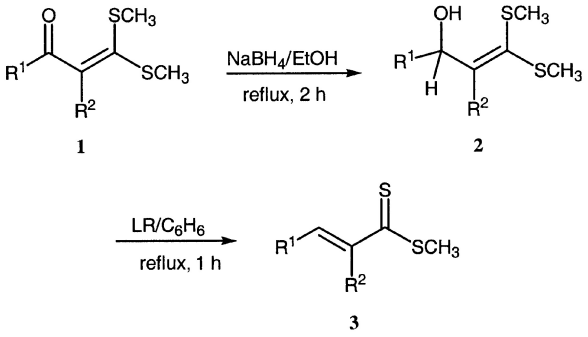
α-Oxoketene dithioacetals are highly versatile building blocks in organic synthesis.[9] The 1,2-reduction[10a] or 1,2-addition of organomagnesium or lithium ragents[10b,c] to α-oxoketene dithioacetals lead to the formation of α-hydroxyketene dithioacetals. Acid catalyzed partial hydrolysis or solvolysis of these carbinols affords α,β-unsaturated thioesters or esters respectively.[10d,11] We have recently developed several methods for the conversion of α-oxoketene dithioacetals to the corresponding β-keto thiolesters[12] or β-keto dithioesters[13] under solvolytic conditions. A base induced demethylation of these building blocks also gave the corresponding dithioesters[14] and this method was further extended to the synthesis of dihydrothiopyrans using alkenoyl ketene dithioacetals.[15] We now report that α-oxoketene dithioacetals can be efficiently used for the preparation of α,β-unsaturated dithioesters as well.

The α-hydroxyketene dithioacetals **2a–e**, derived from aroyl ketene dithioacetals **1a–e**, by a regioselective addition of sodium borohydride to the carbonyl group, on treatment with Lawesson's reagent (LR) gave the substituted dithiocinnamates **3a–e** in high yields (Scheme 1). The reaction was carried out with one equivalent of LR in refluxing benzene for one hour. The isolated dithiocinnamates underwent a slow dimerization involving a [4+2] cycloaddition. However, the *p*-chloro-substituted dithiocinnamate **3c** was found to be stable at room temperature for several weeks. The ketene dithioacetal **1e** prepared from α-tetralone was also subjected to sodium borohydride reduction and the resulting carbinol acetal was allowed to react with LR under similar conditions. The corresponding α,β-unsaturated dithioester **3e** was isolated in 87% yield (Scheme 1), which did not dimerize on keeping at room temperature.

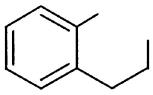
The vinylic protons of the α,β-unsaturated dithioesters **3** appear as doublets having a coupling constant of 15 Hz in the ^{1}H NMR spectra indicating that they exist in the *E* configuration with the bulkier substituents at the β-position *trans* to the dithioester group. The above sequence of reactions was carried out on acyl ketene dithioacetal **1f** also. We could isolate only the dimerized product **4** in 57% yield from this reaction (Scheme 2). This is in accordance with the literature report that methyl dithiocrotonate (**3f**) undergoes facile dimerization to give **4** at room temperature.[3]

α-Oxoketene dithioacetals **1** were also subjected to selective addition of carbon nucleophiles to the carbonyl group and the allylic alcohols obtained were treated with LR. This provides a method for the preparation of β-disubstituted α,β-unsaturated dithioesters. Thus the α-hydroxyketene dithioacetals **5a–e** obtained by the 1,2-addition of methylmagnesium bromide on substituted ketene dithioacetals **1** were treated with LR for one hour. The corresponding α,β-unsaturated dithioesters **6a–e** were obtained in good yields (Scheme 3). The ketene dithioacetal **1e** derived from α-tetralone on 1,2-addition of methyl magne-

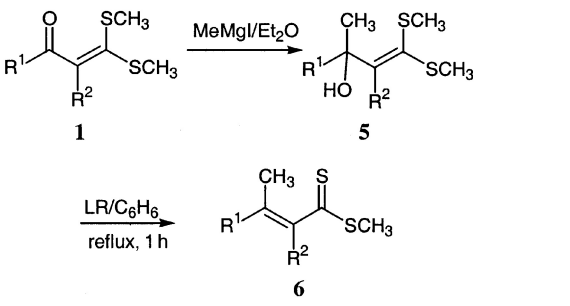
SYNTHESIS 2005, No. 8, pp 1261–1264
Advanced online publication: 07.04.2005
DOI: 10.1055/s-2005-865301; Art ID: T02804SS



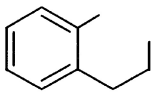
1 2 3

3	R^1	R^2	Yield (%)
a	C_6H_5	H	61
b	4-$CH_3C_6H_4$	H	68
c	4-ClC_6H_4	H	81
d	4-BrC_6H_4	H	68
e			87

Scheme 1



1 5 6

6	R^1	R^2	Yield (%)
a	C_6H_5	H	61
b	4-$CH_3C_6H_4$	H	62
c	4-BrC_6H_4	H	67
d			83
e	CH_3	H	63

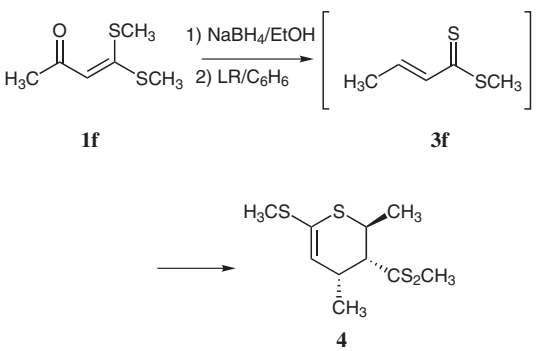
Scheme 3

sium bromide followed by treatment with LR gave 1-methyl-3,4-dihydronaphthalene-2-carbodithioate (**6d**) in 83% yield (Scheme 3). The α,β-unsaturated dithioesters **6a–e**, which are disubstituted at the β-position, are fairly stable at room temperature and do not undergo any appreciable dimerization.

In most of the known methods[7] of preparation of α,β-unsaturated dithioesters **9** starting from carbonyl compound **7**, the dithioester functionality is introduced along with the α-methylene group to form **8**. The present method provides an opportunity to introduce dithioester functionality at the α position of the carbonyl group of the starting ketone to afford **9** (Scheme 4).

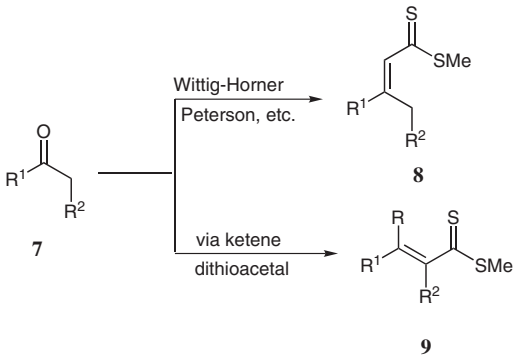
In conclusion, we have developed a facile two step process for the conversion of α-oxoketene dithioacetals to α,β-unsaturated dithioesters, which are valuable intermediates in organic synthesis and the method described here provides a valuable alternative to the previous methods for the synthesis of these compounds. Attempts to synthesize heterocycles of potential applications using the prepared α,β-unsaturated dithioesters are currently underway in our laboratory.

Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker WM 300 MHz NMR spectrometer in $CDCl_3$ solution. Electron impact mass spectra were obtained on a Finnigan-MAT 312 spectrometer. Elemental analyses were done on an Elementar Vario EL III Carlo Erba 1108 instrument. Column chromatography was performed on silica gel (60–120 mesh). All reactions were carried out in an efficient chemical fume hood in benzene (**Caution!** carcinogenic) under N_2 and in flame dried glassware. α-Oxoketene dithioacetals **1** were prepared following reported procedures.[9]



1f 3f 4

Scheme 2



7 8 9

Scheme 4

α,β-Unsaturated Dithioesters 3; General Procedure
$NaBH_4$ (30 mmol, 0.72 g) was taken in absolute EtOH (30 mL). α-Oxoketene dithioacetal **1** (10 mmol) was added and the mixture was refluxed for 1 h. The contents were poured into cold aq sat. solution of NH_4Cl (100 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL), dried and concentrated. The crude carbinol acetal **2** obtained was taken in benzene (50 mL) and to this solution was added LR (10 mmol, 4.04 g). The mixture was refluxed for 1 h, cooled and filtered. The benzene was removed under vacuum and the crude dithioester was purified by flash column chromatography over silica gel using hexanes as the eluent.

Methyl (*E*)-3-Phenylprop-2-enedithioate (3a)
Yield: 1.18 g (61%); red viscous liquid.

Spectral data have been previously reported.[8]

Methyl (*E*)-3-(4-Methylphenyl)prop-2-enedithioiate (3b)
Yield: 1.41 g (68%); red viscous liquid.

IR (neat): 1595, 1510, 1415, 1035, 950 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.69 (s, 3 H), 7.17 (d, 2 H, *J* = 9 Hz), 7.37 (d, 1 H, *J* = 15 Hz), 7.45 (d, 2 H, *J* = 9 Hz), 7.74 (d, 1 H, *J* = 15 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.2, 124.6, 128.3, 128.7, 129.4, 132.1, 137.5, 223.6 (C=S).

Anal. Calcd for $C_{11}H_{12}S_2$: C, 63.41; H, 5.81. Found: C, 63.28; H, 5.61.

Methyl (*E*)-3-(4-Chlorophenyl)prop-2-enedithioate (3c)
Yield: 1.41 g (81%); red needles; mp 77–79 °C.

IR (KBr): 1580, 1485, 1410, 1195, 1010, 940 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.70 (s, 3 H), 7.26 (d, 1 H, *J* = 8.5 Hz), 7.32 (d, 1 H, *J* = 15 Hz), 7.44 (d, 2 H, *J* = 8.5 Hz), 7.64 (d, 1 H, *J* = 15 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 129.3, 129.6, 133.3, 136.1, 223.1.

EIMS: *m*/*z* (%) = 228 (M^+, 28.7), 181 (100), 145 (20.3).

Anal. Calcd for $C_{10}H_9ClS_2$: C, 52.50; H, 3.97. Found: C, 52.54; H, 3.76.

Methyl (*E*)-3-(4-Bromophenyl)prop-2-enedithioate (3d)
Yield: 1.86 g (68%); red viscous liquid.

IR (KBr): 1585, 1560, 1480, 1250, 1000 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.74 (s, 3 H), 7.38 (d, 1 H, *J* = 15 Hz), 7.44 (d, 2 H, *J* = 8.7 Hz), 7.50 (d, 2 H, *J* = 8.7 Hz), 7.70 (d, 1 H, *J* = 15 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 124.4, 129.7, 133.3, 133.7, 136.1, 223.0.

Anal. Calcd for $C_{10}H_9BrS_2$: C, 43.96; H, 3.32. Found: C, 43.90; H, 3.76.

Methyl 3,4-Dihydronaphthalene-2-carbodithioate (3e)
Yield: 1.91 g (87%); red viscous liquid.

IR (KBr): 1595, 1550, 1445, 1170, 1055 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3 H), 2.83–2.88 (m, 2 H), 2.95–3.00 (m, 2 H), 7.13–7.26 (m, 4 H), 7.59 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 28.1, 28.6, 127.3, 128.0, 129.7, 130.0, 130.8, 133.4, 137.9, 144.5, 227.6.

Anal. Calcd for $C_{12}H_{12}S_2$: C, 65.41; H, 5.49. Found: C, 65.18; H, 5.35.

Methyl 2,4-Dimethyl-6-methylthio-2*H*-3,4-dihydrothiopyran-dithiocarboxylate (4)
Yield: 710 mg (57%); red viscous liquid.

Spectral data have been previously reported.[3]

α,β-Unsaturated Dithioesters 6; General Procedure
To a well-cooled (0–5 °C) solution of methylmagnesium bromide (15 mmol) in anhyd Et_2O, was added ketene dithioacetal **1** (10 mmol) in Et_2O (50 mL) slowly over 15 min. The mixture was stirred at this temperature for half an hour and was poured into cold aq sat. NH_4Cl solution (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O and dried. Et_2O was removed and the crude carbinol acetal **5** was taken in benzene[16] (50 mL) and to this solution was added Lawesson's Reagent (4.04 g, 10mmol). The mixture was refluxed for 1 h with stirring. After the reaction, the mixture was cooled and was filtered. The filtrate was washed with H_2O, dried and concentrated. The crude dithioester was purified by column chromatography over silica gel using hexanes as the eluent.

Methyl (*E*)-3-Phenyl-3-methylprop-2-enedithioate (6a)
Yield: 1.27 g (61%); red viscous liquid.

IR (neat): 1590, 1565, 1440, 1220, 1020, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.55 (s, 3 H), 6.97 (s, 1 H), 7.13–7.25 (m, 3 H), 7.34–7.45 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 28.6, 126.50, 128.4, 128.7, 132.6, 143.1, 147.7, 225.0.

Anal. Calcd for $C_{11}H_{12}S_2$: C, 63.41; H, 5.81. Found: C, 63.70; H, 5.82.

Methyl (*E*)-3-(4-Methylphenyl)-3-methylprop-2-enedithioate (6b)
Yield: 1.38 g (62%); red viscous liquid.

IR (neat): 1585, 1550, 1505, 1440, 1210, 1020, 910 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.57 (s, 3 H), 2.66 (s, 3 H), 7.10 (s, 1 H), 7.16 (d, 2 H, *J* = 8.5 Hz), 7.42 (d, 2 H, *J* = 8.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 21.2, 125.7, 126.4, 129.5, 132.0, 138.9, 148.0, 224.9.

Anal. Calcd for $C_{12}H_{14}S_2$: C, 64.82; H, 6.35. Found: C, 64.86; H, 6.41.

Methyl (*E*)-3-(4-Bromophenyl)-3-methylprop-2-enedithioate (6c)
Yield: 1.92 g (67%); red viscous liquid.

IR (neat): 1580, 1480, 1210, 1005 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.65 (s, 3 H), 6.98 (s, 1 H), 7.35 (d, 2 H, *J* = 9 Hz), 7.47 (d, 2 H, *J* = 9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 29.7, 125.8, 128.1, 129.55, 131.6, 132.7, 145.8, 224.9.

Anal. Calcd For $C_{11}H_{11}BrS_2$: C, 46.00; H, 3.86. Found: C, 45.86; H, 3.76.

Methyl 1-Methyl-3,4-dihydronaphthalene-2-carbodithioate (6d)
Yield: 1.94 g (83%); red needles; mp 58–59 °C.

IR (KBr): 1595, 1480, 1445, 1280, 1095, 1040 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.81–2.89 (m, 2 H), 2.93 (s, 3 H), 3.08–3.15 (m, 2 H, 7.38–7.51 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 20.3, 29.1, 30.7, 124.4, 127.0, 127.8, 127.9, 128.0, 135.9, 136.2, 143.4, 237.2.

EIMS: *m/z* = 234 (M^+, 20.5), 187 (59.6), 128 (37.7), 115 (40.2).

Anal. Calcd for $C_{13}H_{14}S_2$: C, 66.62; H, 6.02. Found: C, 67.00; H, 6.02.

Methyl 3-Methylbut-2-enedithioate (6e)
Yield: 920 mg (63%); red viscous liquid.

IR (neat): 1610, 1440, 1420, 1240, 1180, 1020 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 3 H), 2.18 (s, 3 H), 2.55 (s, 3 H), 6.67 (s 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 21.6, 29.2, 131.5, 148.4, 225.8.

Anal. Calcd for $C_6H_{10}S_2$: C, 49.27; H, 6.89. Found: C, 49.58; H, 6.98.

Aknowledgment

This work was supported by the Kerala State CSTE foundation. SKN and ANJ thank UGC and MG University for research fellowships respectively. We are grateful to Dr. Prakash Chandran (POSTECH, South Korea) and Professor S. Perumal (Madurai Kamaraj University) for providing spectral and analytical data.

References

(1) (a) Metzner, P. *Top. Curr. Chem.* **1999**, *204*, 127. (b) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (c) Barluenga, J.; Tomas, M. *Adv. Heterocycl. Chem.* **1993**, *57*, 1.
(2) (a) Vedejs, E.; Stults, J. S. *J. Org. Chem.* **1988**, *53*, 2226. (b) Pinto, I. L.; Buckle, D. R.; Rami, H. K.; Smith, D. G. *Tetrahedron Lett.* **1992**, *33*, 7597. (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Bonini, B. F.; Giannetto, P.; Nicolò, F. *Tetrahedron: Asymmetry* **1999**, *10*, 3919.
(3) Al-Badri, H.; Collignon, N.; Maddaluno, J.; Masson, S. *Tetrahedron* **2000**, *56*, 3909.
(4) Westmijze, H.; Kleijn, H.; Miejer, J.; Vermeer, P. *Synthesis* **1979**, 432.
(5) Gosselin, P.; Masson, S.; Thuillier, A. *Tetrahedron Lett.* **1980**, *21*, 2421.
(6) (a) Masson, S.; Thuillier, A. *Tetrahedron Lett.* **1982**, *23*, 4087. (b) Rettberg, N.; Wagner, U.; Hartke, K. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 977. (c) Lawson, K. R.; Singleton, A.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 859.
(7) Hartke, K.; Kunze, O. *Liebigs Ann. Chem.* **1989**, 321.
(8) Hoffman, R.; Hartke, K. *Chem. Ber.* **1980**, *113*, 919.
(9) (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029. (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423. (c) Kolb, M. *Synthesis* **1990**, 171.
(10) (a) Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 3969. (b) Dieter, R. K.; Jenkitkasemwong, Y.; Dieter, L. W. *J. Org. Chem.* **1984**, *49*, 3183. (c) Dieter, R. K.; Jenkitkasemwong, Y. *Tetrahedron Lett.* **1982**, *23*, 3747. (d) Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5327.
(11) (a) Myrboh, B.; Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50. (b) Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 163. (c) Singh, G.; Purkayastha, M. L.; Ila, H.; Junjappa, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1289. (d) Dieter, R. K.; Dieter, J. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1378.
(12) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **2001**, *31*, 1453.
(13) Nair, S. K.; Asokan, C. V. *Synth. Commun.* **1999**, *29*, 791.
(14) Nair, S. K.; Samuel, R.; Asokan, C. V. *Synthesis* **2001**, 573.
(15) Samuel, R.; Nair, S. K.; Asokan, C. V. *Synlett* **2000**, 1804.