A New Two-Step Synthesis of α-Oxoketene *O,N*-Acetals

Jacques Moussounga, James Bouquant*, Josselin Chuche*

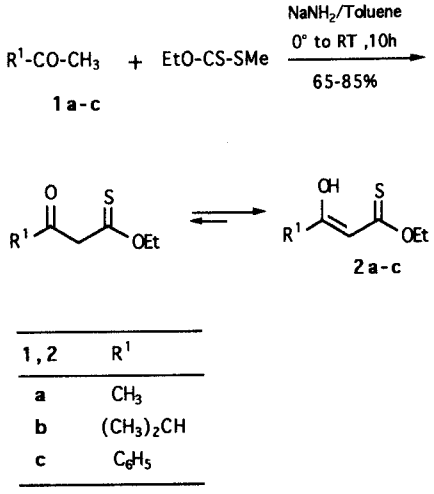
Laboratoire de Chimie Organique Physique, associé au CNRS, Université de Reims-Champagne-Ardenne, BP 347, F-51100 Reims, France

Received 10 May 1993; revised 9 November 1993

A new synthesis of α-oxoketene *O,N*-acetals has been developed from β-oxothioxo esters. Thus, the reaction of **2a–c** with alkyl, allyl or cyclic primary amines in refluxing toluene and formic acid led to α-oxoketene *O,N*-acetals **3a–i** in good yields.

It is well known that α-oxoketene X,Y-acetals (with X and/or Y = S, N, O) are useful intermediates for the construction of a large number of heterocycles.[1,2] In this area, *O,N*-acetals have been much less studied. To our knowledge, they have only been prepared from the corresponding *O,O*-acetals;[3] moreover, their intermediate formation has been suggested in the preparation of alkoxypyrimidines from α-oxoketene *S,S*-acetals and amidines in methanol.[4] In connection with a programme devoted to the thermal generation of α-iminothioketenes[5] enaminothioxo esters were needed. Initially we tried to prepare these compounds by condensation of primary amines with β-oxothioxo esters, a method that has already been used for the synthesis of ester and dithioester analogs.[6] In fact our attempts were unsucessful, but a new method for the preparation of α-oxoketene *O,N*-acetals involving the reaction of β-oxothioxo esters with primary amines was discovered. We report herein the result of this investigation.

Starting, thioxo esters **2a–c** were easily prepared according to an earlier reported procedure[7] by ethoxythiocarbonylation of enolates with *S*-methyl *O*-ethyl dithiocarbonates using toluene as solvent and sodium amide as base to form the enolate (Scheme 1). We found that the use of *S*-methyl instead of *S*-ethyl *O*-ethyl dithiocarbonate led to better yields. The structure of thioesters **2a–c** was confirmed by microanalyses and spectroscopic data (Table 1). It is noteworthy that thioxo esters **2a–c** are highly enolized and only traces of ketonic tautomers could be detected by IR and ^{1}H NMR spectroscopy.[8,9]



1,2	R^1
a	CH_3
b	$(CH_3)_2CH$
c	C_6H_5

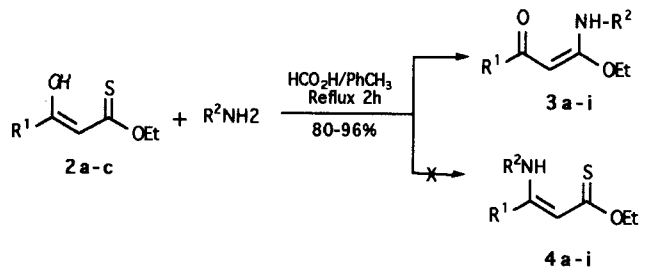
Scheme 1

In a typical experiment, **2a** was reacted with propylamine in refluxing toluene in the presence of formic acid and, after workup and purification, the α-oxoketene *O,N*-acetal **3a** was isolated in 86% yield (Scheme 2). The structure of **3a** was confirmed with the help of analytical and spectral data (Table 2). In particular, the enaminothioxo ester structure **4a** could be ruled out on the basis of microanalytical data; moreover, the ^{1}H and ^{13}C chemical shifts for **3a** were in agreement with the expected values. The deshielded peak of amino protons at δ = 10.55 due to hydrogen bonding between NH and C=O is indicative of an *E*-configuration for the double bond.[10] Moreover, the ^{1}H NMR spectrum of **3a** after workup did not show any trace of **4a**. The hitherto unreported compounds **3b–i** were similarly obtained in good yields from **2a–c**.

Table 1. Compounds **2** Prepared

Product[a]	Yield[b] (%)	bp (°C)/ Torr[c]	Lit. bp (°C)/ Torr	IR ($CHCl_3$) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (M^+)
2a	76	30–32/ 0.1	48/0.8[8]	1716, 1600	1.4 (t, 3H, J = 7.0, $OCH_2\underline{CH_3}$), 2.0 (s, 3H, CH_3), 4.45 (q, 2H, J = 7.0, OCH_2), 5.15 (s, 1H, =CH), 13.75 (s, 1H, OH)	13.4 ($OCH_2\underline{CH_3}$), 22.9 (CH_3), 65.1 (OCH_2), 102.9 (=CH), 177.0 (C=CH), 208.2 (C=S)	146
2b	65	41–42/ 0.1		1710, 1590	1.15 [d, 6H, J = 7.2, $(\underline{CH_3})_2CH$], 1.4 (t, 3H, J = 7.0, $OCH_2\underline{CH_3}$), 2.4 [sept, 1H, J = 7.2, $(CH_3)_2\underline{CH}$], 4.5 (q, 2H, J = 7.0, OCH_2), 5.7 (s, 1H, =CH), 13.8 (s, 1H, OH)	13.7 ($OCH_2\underline{CH_3}$), 19.8 [$(\underline{CH_3})_2CH$], 35.5 [$(CH_3)_2\underline{CH}$], 65.1 (OCH_2), 100.3 (=CH), 185.1 (C=CH), 208.8 (C=S)	174
2c	85	101–103/ 0.1	122–125/ 0.5[8]	1685, 1600	1.4 (t, 3H, J = 7.0, $OCH_2\underline{CH_3}$), 4.55 (q, 2H, J = 7.0, OCH_2), 6.5 (s, 1H, =CH), 7.45 (m, $3H_{arom}$), 7.8 (m, $2H_{arom}$), 14.15 (s, 1H, OH)	13.7 ($OCH_2\underline{CH_3}$), 65.4 (OCH_2), 100.6 (=CH), 126.1 (C_{arom}), 128.5 (C_{arom}), 131.4 (C_{arom}), 134.4 (C_{arom}), 172.4 (C=CH), 208.2 (C=S)	208

[a] Satisfactory microanalyses obtained for all new compounds: C ± 0.17, H ± 0.24, S ± 0.25.
[b] Yield of pure isolated product.
[c] All products were obtained as yellow oils.



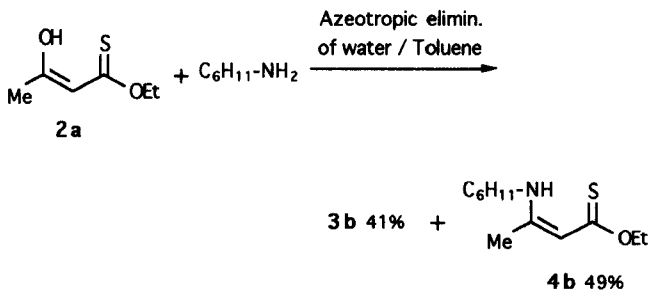
2	R^1	3	R^1	R^2	3	R^1	R^2	3	R^1	R^2
a	CH_3	a	CH_3	n-C_3H_7	d	CH_3	CH_3	g	C_6H_5	CH_3
b	$(CH_3)_2CH$	b	CH_3	C_6H_{11}	e	$(CH_3)_2CH$	C_2H_5	h	C_6H_5	Allyl
c	C_6H_5	c	CH_3	C_2H_5	f	$(CH_3)_2CH$	C_6H_{11}	i	C_6H_5	C_6H_{11}

Scheme 2

Since it is known that the attack at C-1 or C-3 in β-oxo esters depends on the reaction medium and the reaction conditions,[11] we wondered if it would be possible to modify the regioselectivity of the condensation by conducting the reaction without formic acid. In fact, when α-oxoketene **2a** was reacted with cyclohexylamine in refluxing toluene, a mixture of α-oxoketene *O,N*-acetal **3b** and *O*-ethyl 3-*N*-cyclohexylamino-2-butenethioate **(4b)** was obtained after azeotropic elimination of water (Scheme 3). These compounds could be purified by flash chromatography and isolated in 41% and 49% yields, respectively. The structure of **4b** was confirmed with the help of spectral and analytical data. It is very likely that the regioselective formation of α-oxoketene *O,N*-acetals **3a–i** in the presence of formic acid might be explained by protonation of thioxo esters **2a–c** leading to an increased reactivity at C-1 towards nucleophiles.

In conclusion we have devised a new efficient synthesis of α-oxoketene *O,N*-acetals from easily accessible β-oxothioxo esters. Studies on their thermal reactivity are in progress.

Melting points are uncorrected. NMR spectra were recorded on a Bruker AC-300 instrument at 300 MHz for ^1H and 75.5 MHz for ^{13}C with TMS (δ = 0.00) and $CDCl_3$ (δ = 77.00) as internal standards, respectively. IR spectra were recorded on a Philips SP3-300 spectrophotometer. Mass spectra were recorded on a Jeol D-300 mass spectrometer at 70 eV. Compounds were analyzed at the Service Central de Microanalyse du CNRS, Lyon, France and in our laboratory on a Perkin-Elmer CHN-2400 instrument.



Scheme 3

The required *S*-methyl *O*-ethyl dithiocarbonates were prepared according to an earlier reported procedure.[12]

O-Ethyl 3-Oxo-2-butenethioate (2a); Typical Procedure:
A mixture of *S*-methyl *O*-ethyl dithiocarbonate (13.6 g, 100 mmol) and ketone **1a** (5.8 g, 100 mmol) was added dropwise to a well-stirred suspension of $NaNH_2$ (7.8 g, 200 mmol) in toluene (100 mL) cooled at 0 °C. Then, the temperature of the mixture was raised to r.t. and stirring was continued for 10 h. The mixture was poured into ice-cold water (200 mL) acidified with dilute HCl (10%) and extracted with Et_2O (100 mL). The organic layer was washed with sat. aq NaCl (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (200 g) eluting with EtOAc/petroleum ether (bp 60 °C) (15:85) to give analytically pure **2a**.

O-Ethyl-N-Propylamino-3-oxobutylketene Acetal (3a); Typical Procedure:
Formic acid (5 drops, 0.14 mmol) was added to a solution of **2a** (2.92 g, 20 mmol) in toluene (50 mL). Then propylamine (1.41 g, 24 mmol) was added dropwise to the mixture. After refluxing for 2 h, the mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (180 g), eluting with EtOAc/petroleum ether (bp 60 °C) (30:70) to afford analytically pure **3a**; yield: 2.14 g (86%).

O-Ethyl 3-N-Cyclohexylamino-2-butenethioate (4b):
A solution of **2a** (2.92 g, 20 mmol) in toluene (50 mL) and a solution of cyclohexylamine (2.37 g, 24 mmol) in toluene (10 mL) were successively introduced into a round bottomed flask fitted with a Dean–Stark apparatus. After refluxing for 2.5 h, the mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (180 g). Elution with EtOAc/petroleum ether (bp 60 °C) (10:90, 500 mL) afforded analytically pure **4b**; yield: 2.22 g (49%); bp 78–79 °C/0.1 Torr. Elution with a more polar solvent (EtOAc/petroleum ether (bp 60 °C), 30:70, 600 mL) afforded the analytically pure α-oxoketene *O,N*-acetal **3b**; yield: 1.73 g (41%).

4b:

$C_{11}H_{21}NSO$ (215.3) calc. C 63.69 H 9.31 N 6.16 S 14.10
found 63.63 9.47 6.11 13.86

^1H NMR ($CDCl_3$): δ = 1.35 (t, 3H, $OCH_2\underline{CH}_3$), 1.40 (m, 4H, $2CH_2$), 1.60 (m, 2H, CH_2), 1.85 (m, 4H, $2CH_2$), 2.05 (s, 3H, CH_3), 3.55 (s, 1H, CH), 4.40 (q, 2H, CH_2), 5.40 (s, 1H, CH), 11.6 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): δ = 14.1 (q, $OCH_2\underline{C}H_3$), 20.4 (CH_3), 24.0 (CH_2), 25.1 (CH_2), 33.3 (CH_2), 52.01 (CH), 63.0 (t, OCH_2), 98.5 (d, CH=), 162.2 (s, $\underline{C}$=CH), 202.2 (C=S).

MS (70 eV): *m/z* (%) = 211 (M^+ +, 31), 182 (30), 102 (33), 98 (100), 85 (55), 56 (10).

(1) For reviews on α-oxoketene *S,S*-acetals and related compounds in heterocyclic synthesis, see:
Dieter, R.K. *Tetrahedron* **1986**, *42*, 3029.
Kolb, M. *Synthesis* **1990**, 171.
(2) Satyanarayana, J.; Ila, H. Junjappa, H. *Synthesis* **1991**, 889.
Kumar, H.; Ila, H.; Junjappa, H. *Synthesis* **1980**, 748.
(3) Stachel, H.D. *Chem. Ber.* **1960**, *93*, 1059.
Hojo, M.; Masuda, R.; Okada, E.; Yamamoto, H.; Morimoto, K.; Okada, K. *Synthesis* **1990**, 195.
(4) Chauhan, S.M.S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779.
(5) Moussounga, J.; Bouquant, J.; Chuche, J., unpublished results.
(6) Werner, W. *Tetrahedron* **1969**, *25*, 1969.
Le Coustumer, G.; Mollier, Y. *Bull. Soc. Chim. Fr.* **1973**, 3349.
(7) Scheithauer, S.; Pech, H. German Patent 94, 361 (1972); *Chem. Abstr.* **1973**, *79*, 5176.
(8) Palominos, M.A.; Rodriguez, R.; Vega, J.C. *Chem. Lett.* **1986**, 1251.

Table 2. α-Oxoketene *O,N*-acetals **3a–i** Prepared

Product[a]	Yield (%)	mp (°C) or bp (°C)/Torr	IR (CH_2Cl_2) ($CHCl_2$) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
3a	86	66–68/ 0.1	3150, 2980, 2950, 1615, 1550, 1510	0.9 (t, 3H, J= 7.0, CH_3), 1.35 (t, 3H, J= 7.0, OCH_2CH_3), 1.6 (m, 2H, CH_2), 2.05 (s, 3H, CH_3CO), 3.2 (q, 2H, J= 7.0, NCH_2), 4.05 (q, 2H, J= 7.0, OCH_2), 4.7 (s, 1H, =CHCO), 10.55 (br s, 1H, NH)	11.0 (CH_3), 13.9 (OCH_2CH_3), 22.7 (NCH_2CH_2), 28.6 (CH_3CO), 41.2 (NCH_2), 63.6 (OCH_2), 76.0 (=CHCO), 167.2 (NCH=), 192.0 (C=O)	171 (M^+, 23), 128 (96), 100 (100), 58 (57)
3b	86	58–59	3107, 2980, 2940, 1610, 1550, 1510	1.3 (m, 4H, $2CH_2$), 1.4 (t, 3H, J= 7.0, OCH_2CH_3), 1.55 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 2.05 (s, 3H, CH_3CO), 3.15 (m, 1H, NCH), 4.05 (q, 2H, J= 7.0, OCH_2), 4.7 (s, 1H, =CHCO), 10.6 (br s, 1H, NH)	14.2 (OCH_2CH_3), 24.2 (CH_2), 25.3 (CH_2), 28.8 (CH_3CO), 32.9 (CH_2), 48.4 (CH), 63.7 (OCH_2), 76.1 (=CHCO), 166.6 (NCH=), 192.1 (C=O)	211 (M^+, 35), 182 (30), 102 (38), 98 (100), 85 (58)
3c	96	61–63/ 0.1	3126, 2960, 1595, 1550, 1500	0.6 (m, 2H, CH_2), 0.7 (m, 2H, CH_2), 1.4 (t, 3H, J= 7.0, OCH_2CH_3), 2.0 (s, 3H, CH_3CO), 2.65 (m, 1H, NCH), 4.05 (q, 2H, J= 7.0, OCH_2), 4.7 (s, 1H, =CHCO), 10.4 (br s, 1H, NH)	6.5 (CH_2), 14.2 (OCH_2CH_3), 22.3 (CH), 28.9 (CH_3CO), 64.0 (OCH_2), 76.6 (=CHCO), 168.8 (NCH=), 192.7 (C=O)	169 (M^+, 24), 140 (60), 112 (44), 85 (92), 57 (65), 56 (100)
3d	90	66–67	3148, 2980, 1620, 1550, 1510	1.4 (t, 3H, J= 7.0, OCH_2CH_3), 2.1 (s, 3H, CH_3CO), 2.85 (d, 3H, J= 5, CH_3N), 4.05 (q, 2H, J= 7.0, OCH_2), 4.7 s, 1H, =CHCO), 10.4 (br s, 1H, NH)	14.1 (OCH_2CH_3), 26.0 (CH_3CO), 28.7 (CH_3N), 63.8 (OCH_2), 76.5 (=CHCO), 167.9 (NCH=), 192.2 (C=O)	143 (M^+, 100), 100 (95), 85 (79), 74 (48), 58 (83)
3e	82	58–60/ 0.1	3150, 2960, 1610, 1540, 1505	1.1 [d, 6H, J= 7.2, $(CH_3)_2CH$], 1.2 (t, 3H, J= 7.0, CH_3), 1.4 (t, 3H, J= 7.0, OCH_2CH_3), 2.4 [sept, 1H, J= 7.2 $(CH_3)_2CH$], 3.3 (m, 2H, NCH_2), 4.05 (q, 2H, J= 7.0, OCH_2), 4.7 (s, 1H, =CHCO), 10.5 (br s, 1H, NH)	14.2 (OCH_2CH_3), 14.8 (NCH_2CH_3), 20.0 [$(CH_3)_2CH$], 34.6 (NCH_2), 39.7 [$(CH_3)_2CH$], 63.8 (OCH_2), 73.9 (=CHCO), 167.8 (NCH=), 199.8 (C=O)	185 (M^+, 53), 157 (95), 128 (100), 99 (32), 69 (38), 58 (97)
3f	88	87–89/ 0.1	3113, 2960, 2920, 1600, 1540, 1505	1.1 [d, 6H, J= 7.2, $(CH_3)_2CH$], 1.3 (m, 4H, CH_2), 1.4 (t, 3H, OCH_2CH_3), 1.5 (m, 2H, CH_2), 1.7 (m, 2H, CH_2), 1.9 (m, 2H, CH_2), 2.4 [sept, 1H, J= 7.2, $(CH_3)_2CH$], 3.6,(m, 1H, NCH), 4.05 (q, 2H, OCH_2), 4.7 (s, 1H, =CHCO), 10.6 (br s, 1H, NH)	14.3 (OCH_2CH_3), 20.0 [$(CH_3)_2C$], 24.4 (CH_2), 25.4 (CH_2), 33.0 (CH_2), 39.7 [$(CH_3)_2CH$], 48.7 (CH), 63.7 (OCH_2), 73.8 (=CHCO), 167.1 (=CHN), 199.6 (C=O)	239 (M^+, 20), 169 (100), 102 (25), 83 (40), 55 (30)
3g	96	53–54	3180, 2960, 1600, 1580, 1510	1.4 (t, 3H, J= 7.0, OCH_2CH_3), 2.9 (d, 3H, J= 5, NCH_3), 4.15 (q, 2H, J= 7.0, OCH_2), 5.4 (s, 1H, =CHCO), 7.4 (m, $3H_{arom}$), 7.8 (m, $2H_{arom}$), 10.9 (br s, 1H, NH)	14.2 (OCH_2CH_3), 26.3 (NCH_3), 64.1 (OCH_2), 73.8 (=CHCO), 126.4 (C_{arom}), 127.9 (C_{arom}), 129.9 (C_{arom}), 140.9 (C_{arom}), 168.9 (=CHN), 186.2 (C=O)	205 (M^+, 10), 191 (70), 114 (70), 105 (100), 77 (72)
3h	84	51–52	3140, 2995, 1620, 1580, 1520, 1470	1.4 (t, 3H, J= 7.0, OCH_2CH_3), 3.95 (m, 2H, CH_2N), 4.15 (q, 2H, OCH_2), 5.25 (m, 2H, CH_2=CH), 5.4 (s, 1H, =CHCO), 7.4 (m, $3H_{arom}$), 7.8 (m, $2H_{arom}$), 11.5 (br s, 1H, NH)	14.2 (OCH_2CH_3), 42.3 (NCH_2), 64.2 (OCH_2), 73.9 (=CHCO), 115.8 (CH_2=CH), 126.4 (C_{arom}), 127.9 (C_{arom}), 130.0 (C_{arom}), 133.7 (CH_2=CH), 140.8 (C_{arom}), 168.3 (=CHN), 186.5 (C=O)	231 (M^+, 20), 202 (19), 147 (22), 105 (98), 77 (65)
3i	85	37–38	3123, 2960, 1585, 1565, 1500	1.3 (m, 4H, CH_2), 1.4 (t, 3H, J= 7.0, OCH_2CH_3), 1.6 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 1.9 (m, 2H, CH_2), 3.7 (m, 1H, NCH), 4.15 (q, 2H, J= 7.0, OCH_2), 5.35 (s, 1H, =CHCO), 7.4 (m, $3H_{arom}$), 7.9 (m, $2H_{arom}$), 11.2 (br s, 1H, NH)	14.2 (OCH_2CH_3), 24.2 (CH_2), 25.3 (CH_2), 32.9 (CH_2), 48.7 (CH), 64.0 (OCH_2), 73.5 (=CHCO), 126.4 (C_{arom}), 127.8 (C_{arom}), 129.8 (C_{arom}), 140.9 (C_{arom}), 167.5 (=CHN), 185.9 (C=O)	273 (M^+, 32), 244 (50), 164 (30), 147 (100), 105 (100), 77 (75)

[a] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.28, N ± 0.29. [b] Yield of pure isolated product.

(9) Purkayastha, M.L.; Chandrasekharam, M.; Vishwakarma, J.N.; Ila, H.; Junjappa, H. *Synthesis* **1993**, 245.
(10) Huang, Z.T.; Shi, S. *Synthesis* **1990**, 162.
(11) Katritzky, A.R.; Barczynski, P.; Ostercamp, D.L.; Yousaf, T.I. *J. Org. Chem.* **1986**, *51*, 4037.
Jacobsen, N.; Kolind-Andersen, H. Christensen, H.J. *Can. J. Chem.* **1984**, *62*, 1940.
(12) Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1979**, 178.