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MILD SYNTHESIS OF α-OXOKETENE *O,N*-ACETALS FROM β-OXOTHIOXO ESTERS AND AMINES

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Abstract: α-Oxoketene *O,N*-acetals were prepared from β-oxothiono esters and primary amines in the presence of triethylamine at room temperature within several hours in good yields.

α-Oxoketene *X,Y*-acetals (X,Y = S, N, O) are interesting starting materials for the synthesis of carbocycles,[1,2] heterocycles,[1,2a,3] polyenes,[4] and aldol products.[1,2,5] Although their usability, *O,N*-acetal derivatives are still room for developing synthetic methods and their applications.[6] There are few reports for the

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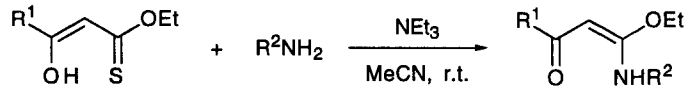
synthesis of such type of compounds from α-oxoketene *O,O*- and *S,S*-acetals and amines.[7] Recently, a new pathway for the preparation of them from β-oxothiono esters[8] and amines was reported.[9] This has an advantage of using conventional starting materials but needs formic acid and heating to result formation of a perilly and a bad-smelling hydrogen sulfide[10] as a by-product.

Now we report a modified method under mild conditions for the preparation of α-oxoketene *O,N*-acetals from β-oxothiono esters and amines in the presence of triethylamine.



1 2 3

65–99%

R^1 = Me, $(Me)_3C$, Ph, *p*-$MeOC_6H_4$, *p*-ClC_6H_4
R^2 = Me, Et, *n*-Pr, *i*-Pr, $PhCH_2$

In acetonitrile (10 mL), a mixture of an equimolar amount of β-oxothiono ester (1.0 mmol) and primary amine in the presence of triethylamine (1.0 mmol) was allowed to react for 0.5–2 h, giving an α-oxoketene *O,N*-acetal in good to excellent yield. Several substituents for R^1 and R^2 used did not affect yields of the products (Table 1). The products were identified by comparison of analytical data to authentic samples published in literature and/or prepared according to the literature method.[9]

In the preparation of *N*-methyl and *N*-ethyl derivatives, their hydrogen chloride salts were used instead of amines (R^2 = Me and Et) because of their volatility and low boiling points, and 2 equivalent of triethylamine was used as well. This reaction was limited for primary amines. When secondary amines were employed, reaction was very slow to give a trace amount of products. Without triethylamine, the yield of the product decreased.

Table 1. Synthesis of α-Oxoketene *O,N*-Acetals **3** from β-Oxothiono Esters **1** and Amines **2**

	R^1	R^2	Yield[a] (%)		R^1	R^2	Yield[a] (%)
3a	Me	Me	84	**3l**	Ph	*i*-Pr	72
3b	Me	Et	74	**3m**	Ph	$PhCH_2$	98
3c	Me	*n*-Pr	99	**3n**	*p*-$MeOC_6H_4$	Me	65
3d	Me	*i*-Pr	99	**3o**	*p*-$MeOC_6H_4$	*n*-Pr	96
3e	Me	Ph	98	**3p**	*p*-$MeOC_6H_4$	*i*-Pr	98
3f	$(Me)_3C$	Me	68	**3q**	*p*-$MeOC_6H_4$	$PhCH_2$	99
3g	$(Me)_3C$	*n*-Pr	99	**3r**	*p*-ClC_6H_4	Me	87
3h	$(Me)_3C$	*i*-Pr	73	**3s**	*p*-ClC_6H_4	*n*-Pr	99
3i	$(Me)_3C$	$PhCH_2$	99	**3t**	*p*-ClC_6H_4	*i*-Pr	95
3j	Ph	Me	67	**3u**	*p*-ClC_6H_4	$PhCH_2$	99
3k	Ph	*n*-Pr	99				

[a] Yield was determined by GC using internal standard method.

This easy and mild synthetic method of α-oxoketene *O,N*-acetals opens the door for the utilization of **3** as substrates for the synthesis of various useful organic compounds. Actually evolution of hydrogen sulfide was very little, and white precipitates were formed, which was considered to be triethylamine–hydrogen sulfide complex. A part of our synthetic utilization of this class of compounds was already reported.[11]

EXPERIMENTAL

All solvents were dried by standard methods. Commercially available compounds were used without further purification. β-Oxothiono esters were

Table 2. Analytical data of α-oxoketene *N*-alkyl *O*-ethyl *O*, *N*-acetals **3**

	IR (cm^{-1})	MS (m/e)	^1H NMR ($CDCl_3$, 400 MHz)
3d	1615, 1090	171	1.20 (6H, d, $NHCH(CH_3)_2$), 1.37 (3H, t, OCH_2CH_3), 2.02 (3H, s, CH_3), 3.92-3.89 (1H, m, NHC*H*), 4.02 (2H, q, OCH_2), 4.67 (1H, s, =C*H*), 10.46 (1H, br, N*H*)
3e	1590, 1095	219	1.32 (3H, t, OCH_2CH_3), 2.05 (3H, s, CH_3), 4.01 (2H, q, OCH_2), 4.44 (2H, d, $NHCH_2$), 4.75 (1H, s, =C*H*), 7.33-7.22 (5H, m, Ar), 10.88 (1H, br, N*H*)
3f	1615, 1095	185	1.15 (9H, s, CH_3), 1.38 (3H, t, OCH_2CH_3), 2.84 (3H, d, $NHCH_3$), 4.05 (2H, q, OCH_2), 4.88 (1H, s, =C*H*), 10.65 (1H, br, N*H*)
3g	1610, 1095	213	0.95 (3H, t, $NH(CH_2)_2CH_3$), 1.15 (9H, s, CH_3), 1.37 (3H, t, OCH_2CH_3), 1.62-1.53 (2H, m, $NHCH_2CH_2$), 3.20 (2H, q, $NHCH_2$), 4.04 (2H, q, OCH_2), 4.86 (1H, s, =C*H*), 10.70 (1H, br, N*H*)
3h	1610, 1078	213	1.15 (9H, s, CH_3), 1.20 (6H, d, $NHCH(CH_3)_2$), 1.37 (3H, t, OCH_2CH_3), 3.93-3.88 (1H, m, NHC*H*), 4.05 (2H, q, OCH_2), 4.83 (1H, s, =C*H*), 10.60 (1H, br, N*H*)
3i	1610, 1092	261	1.15 (9H, s, CH_3), 1.34 (3H, t, OCH_2CH_3), 4.04 (2H, q, OCH_2), 4.43 (2H, d, $NHCH_2$), 4.91 (1H, s, =C*H*), 7.33-7.22 (5H, m, Ar), 11.00 (1H, br, N*H*)
3k	1605, 1120	233	0.99 (3H, t, $NH(CH_2)_2CH_3$), 1.42 (3H, t, OCH_2CH_3), 1.66-1.61 (2H, m, $NHCH_2CH_2$), 3.30 (2H, q, $NHCH_2$), 4.17 (2H, q, OCH_2), 5.37 (1H, s, =C*H*), 7.85-7.36 (5H, m, Ar), 11.05 (1H, br, N*H*)
3l	1600, 1108	233	1.27 (6H, d, $NHCH(CH_3)_2$), 1.42 (3H, t, OCH_2CH_3), 4.03-3.98 (1H, m, NHC*H*), 4.17 (2H, q, OCH_2), 5.35 (1H, s, =C*H*), 7.85-7.36 (5H, m, Ar), 10.96 (1H, br, N*H*)

(continued)

Table 2. Continued.

3m	1590, 1110	—	1.39 (3H, t, OCH_2CH_3), 4.16 (2H, q, OCH_2), 4.53 (2H, d, $NHCH_2$), 5.42 (1H, s, =CH), 7.85-7.25 (10H, m, Ar), 11.39 (1H, br, NH)
3n	1593, 1118	—	1.43 (3H, t, OCH_2CH_3), 2.92 (3H, d, $NHCH_3$), 3.84 (3H, s, OCH_3), 4.16 (2H, q, OCH_2), 5.34 (1H, s, =CH), 7.82-6.89 (4H, m, Ar), 10.84 (1H, br, NH)
3o	1593, 1118	—	0.99 (3H, t, $NH(CH_2)_2CH_3$), 1.42 (3H, t, OCH_2CH_3), 1.67-1.58 (2H, m, $NHCH_2CH_2$), 3.29 (2H, q, $NHCH_2$), 3.84 (3H, s, OCH_3), 4.15 (2H, q, OCH_2), 5.33 (1H, s, =CH), 7.84-6.89 (4H, m, Ar), 10.98 (1H, br, NH)
3p	1593, 1110	—	1.25 (6H, d, $NHCH(CH_3)_2$), 1.42 (3H, t, OCH_2CH_3), 3.84 (3H, s, OCH_3), 4.03-3.95 (1H, m, NHCH), 4.16 (2H, q, OCH_2), 5.31 (1H, s, =CH), 7.83-6.89 (4H, m, Ar), 10.89 (1H, br, NH)
3q	1590, 1115	—	1.38 (3H, t, OCH_2CH_3), 3.84 (3H, s, OCH_3), 4.15 (2H, q, OCH_2), 4.52 (2H, d, $NHCH_2$), 5.39 (1H, s, =CH), 7.84-6.89 (9H, m, Ar), 11.32 (1H, br, NH)
3r	1600, 1083	239	1.44 (3H, t, OCH_2CH_3), 4.16 (3H, d, $NHCH_3$), 4.16 (2H, q, OCH_2), 5.33 (1H, s, =CH), 7.78-7.34 (4H, m, Ar), 10.98 (1H, br, NH)
3s	1603, 1085	267	0.99 (3H, t, $NH(CH_2)_2CH_3$), 1.42 (3H, t, OCH_2CH_3), 1.68-1.59 (2H, m, $NHCH_2CH_2$), 3.30 (2H, q, $NHCH_2$), 4.16 (2H, q, OCH_2), 5.32 (1H, s, =CH), 7.78-7.34 (4H, m, Ar), 11.03 (1H, br, NH)
3t	1603, 1082	267	1.26 (6H, d, $NHCH(CH_3)_2$), 1.43 (3H, t, OCH_2CH_3), 4.07-3.95 (1H, m, NHCH), 4.17 (2H, q, OCH_2), 5.30 (1H, s, =CH), 7.78-7.34 (4H, m, Ar), 10.95 (1H, br, NH)
3u	1600, 1085	—	1.39 (3H, t, OCH_2CH_3), 4.17 (2H, q, OCH_2), 4.53 (2H, d, $NHCH_2$), 5.38 (1H, s, =CH), 7.80-7.27 (9H, m, Ar), 11.36 (1H, br, NH)

prepared according to the literature method.[8,9] Analyses of gas chromatography were performed on a Shimadzu GC-14A (Column packing: 5% Silicone SE-30 on a Chromosorb W AW DMCS (80-100 mesh)).

Typical reaction procedure. In a 25 mL flask was stirred a mixture of *O*-ethyl 3-hydroxy-3-phenyl-2-propenethioate (207 mg, 1.00 mmol), NEt_3 (101 mg, 1.00 mmol), benzylamine (107 mg, 1.00 mmol), and acetonitrile (10 mL) at room temperature for 2 h. After separation of solid materials and concentration, crude product was purified by column chromatography (silica gel, hexane–ethyl acetate) to give a white solid. **3m** (R^1 = Ph, R^2 = $PhCH_2$) 258 mg, 98% yield, mp 71.0–71.5 °C. *N*-Methyl and *N*-ethyl derivatives were prepared by use of their hydrogen chloride salts instead of amine, and also triethylamine added was 2 mmol. Analytical data of new compounds were listed in Table 2. The identifications of these compounds were done by these analytical data of the products by comparison with those of the authentic samples prepared from the literature method,[9] and by the products of the reaction of **3** with maleic anhydride.[11]

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