Reaction of α-Oxo Ketene Dithioacetals with Glycine

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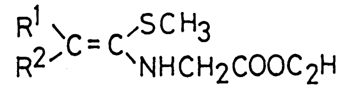
Synopsis. 3-Carboxymethylamino-3-methylthio-1-phenyl-2-propen-1-ones were synthesized by the reaction of 3,3-bis(methylthio)-1-phenyl-2-propen-1-ones with glycine in the presence of sodium hydroxide.

We were interested in studying the polarized α-oxo ketene *N,S*- and *N,N*-acetals, a new class of vinylogous amides, which are versatile synthons used for the synthesis of various heterocyclic compounds.[1] Many displacement reactions of α-oxo ketene dithioacetals[2,3] with nucleophiles have been reported, but there have been few reactions with amino acids mentioned in the literature. Gante et al. described the synthesis of glycine ester derivatives (**1**; R^1=CN, R^2=CN or $COOC_2H_5$) from the bis(methylthio)methylene compounds and glycine ethyl ester.[4] Also, Junjappa et al. reported that the reaction of methyl 2-benzoyldithioacetate with glycine ethyl ester gave *N*-ethoxycarbonylmethyl-2-benzoylthioacetamide, which was converted by methylation into 3-ethoxycarbonylmethylamino-3-methylthio-1-phenyl-2-propen-1-one(**1**; R^1=C_6H_5CO, R^2=H).[5]

In this note we report on a new synthesis of 3-carboxymethylamino-3-methylthio-1-phenyl-2-propen-1-ones (**3**) by a reaction of 3, 3-bis (methylthio)-1-phenyl-2-propen-1-ones (**2**)[6–8] with glycine. The starting materials **2**, including new compounds **2b** and **2e**, were prepared from acetophenones, carbon disulfide, and methyl iodide in the presence of sodium hydride.

The reaction of **2** with glycine was conducted in ethanol–water (10 : 1) in the presence of sodium hydroxide under reflux for 20 h. Double molar quantities of glycine and sodium hydroxide were used; yellow or orange products **3** were obtained in moderate to good



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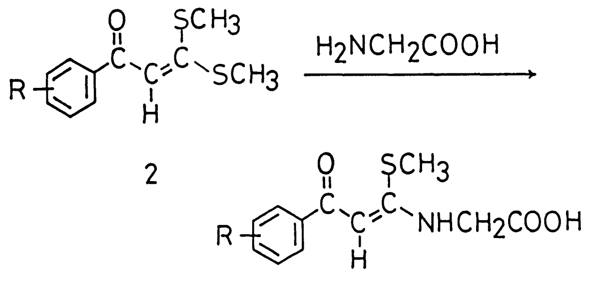

2

3

a : R=H　b : R=3-CH_3
c : R=4-CH_3　d : R=4-CH_3O
e : R=3-NO_2　f : R=4-NO_2

Table 1. Physical Properties and Spectral Data

Compd	Yield[a)] %	Mp[b)] θ_m/°C (Solvent)	IR spectra in KBr (cm^{-1})	UV spectra in EtOH (nm) (log ε)	Molecular formula	Found (Calcd) (%) C	H	N
3a	63 (22)	154—155 (EtOH)	3030—2880 (s) 1730 (vs) 1590 (vs)	248 (4.00), 346 (4.32)	$C_{12}H_{13}NO_3S$	57.52 (57.35)	5.21 (5.21)	5.59 (5.57)
3b	49 (31)	149—150 (EtOH)	3020—2840 (s) 1725 (vs) 1590sh (m)	251 (4.07), 345 (4.34)	$C_{13}H_{15}NO_3S$	58.93 (58.85)	5.70 (5.70)	5.24 (5.28)
3c	50 (29)	158—160 (EtOH)	3020—2840 (s) 1730 (vs) 1608 (s)	254 (4.14), 345 (4.47)	$C_{13}H_{15}NO_3S$	58.83 (58.85)	5.64 (5.70)	5.20 (5.28)
3d	45 (32)	149—150 (EtOH)	3000—2830 (s) 1735 (vs) 1600 (s)	218 (3.99), 223 (3.99), 265 (3.96), 348 (4.50)	$C_{13}H_{15}NO_4S$	55.65 (55.50)	5.33 (5.37)	4.90 (4.98)
3e	74 (6)	171—172 (AcOH)	3060—2880 (s) 1725 (vs) 1608 (s)	230 (4.09), 247sh (3.99), 350 (4.22)	$C_{12}H_{12}N_2O_5S$	48.57 (48.64)	4.13 (4.08)	9.19 (9.45)
3f	81 (0)	193—195 (AcOH)	2950—2800 (s) 1725 (vs) 1600sh (m)	259 (4.18), 295sh (4.01), 374 (4.20)	$C_{12}H_{12}N_2O_5S$	48.64 (48.64)	4.05 (4.08)	9.26 (9.45)

a) The yield in parenthesis refers to that of the recovered starting material **2**. b) Decomposition.

yields. A larger excess of the base resulted in a lower yield and often gave the corresponding acetophenone in a decomposed form. In the absence of sodium hydroxide the yield was only about 3%, and in the case of using triethylamine or sodium acetate used as a base, the reaction hardly proceeded. A reflux time of 20 h was set in order to make comparisons with the substituent effect of the phenyl groups. Nitro derivatives **2e** and **2f** afforded the desired products, **3e** and **3f**, in good yields; from methyl and methoxy compounds **2b**—**d**, however, the glycine derivatives **3b**—**d** were obtained in lower yields and about 30% of the corresponding unreacted starting materials were recovered (Table 1).

The IR spectra of **3** showed a carbonyl absorption of the free carboxyl group at 1725—1735 cm^{-1} as those of other *N*-substituted glycines, *N*-phenylglycine (1720 cm^{-1}) and hippuric acid (1750 cm^{-1}). From the ^{1}H NMR spectrum of **3a** a single structure of *Z*-isomer was derived, which had the same geometry as its ethyl ester **1** (R^1=C_6H_5CO, R^2=H).[5] The spectrum showed a single methyl absorption at δ=2.55 and a triplet assigned to NH at a higher field (δ=1.70). This was due to a non-hydrogen-bonding NH proton to the carbonyl oxygen. The reactions of α-oxo ketene dithioacetals with nucleophiles, just as with organocopper reagents, appear to proceed in a stereoselective fashion, and also to involve an addition-elimination sequence.[2,9] In general, the α-oxo ketene *S,S*-acetals arising from alkyl and aryl ketones react with amines to afford *E*- and *Z*-isomers of the α-oxo ketene *N,S*-acetals, respectively.[2] Thus, our reaction probably led to more stable *Z*-isomers.

Attempts to prepare doubly displaced derivatives using a large excess of glycine were unsuccessful.

Experimental

α-Oxo Ketene Dithioacetals (2) were prepared by the reaction of the corresponding acetophenone (0.057 mol) with carbon disulfide (4.5 g, 0.059 mol) and methyl iodide(18 g, 0.13 mol) in the presence of sodium hydride (5 g; 60% dispersion in oil; 0.13 mol) in tetrahydrofuran (80 ml) with 3 h cooling in ice.

3,3-Bis(methylthio)-1-(*m*-tolyl)-2-propen-1-one(2b): Yellow crystals; yield 83%; mp 82—84 °C (CCl_4-hexane); IR(KBr) 1608s cm^{-1} (C=O); UV(EtOH) λ_{max} 225sh (log ε 3.77), 270sh (3.94), 277sh (3.94), and 345 nm (4.28). Found: C, 60.53;H, 5.94%. Calcd for $C_{12}H_{14}OS_2$: C, 60.47; H, 5.92%.

3,3-Bis(methylthio)-1-(*m*-nitrophenyl)-2-propen-1-one(2e): Yellow crystals; yield 84%; mp 130—131 °C (acetone); IR(KBr) 1615vs cm^{-1} (C=O); UV(EtOH) λ_{max} 240 (log ε 4.21), 287 (3.91), and 353 nm (4.26). Found: C, 49.08; H, 4.10; N, 5.17%. Calcd for $C_{11}H_{11}NO_3S_2$: C, 49.05; H, 4.12; N, 5.20%.

3-Carboxymethylamino-3-methylthio-1-phenyl-2-propen-1-ones (3). General Procedure. A solution of glycine (0.3 g, 0.004 mol) and sodium hydroxide (0.16 g, 0.004 mol) in ethanol (20 ml) and water (2 ml) was refluxed for 1 h. The α-oxo ketene dithioacetal **2** (0.002 mol) was added and the mixture was refluxed for 20 h. After the solvents were evaporated, 10 ml of water was added to the residue, and the mixture was stirred for 30 min. An insoluble solid, **2**, was collected, washed with water, and dried. To the filtrate was added a large excess of dilute hydrochloric acid; the mixture was kept overnight. The yellow or orange precipitate, **3** was collected, washed with water, dried, and recrystallized. In the case of **3e** or **3f**, 20 ml of water was added to the residue described above, and the mixture was stirred with warming. The collected **2e** was washed with hot water. Compound **2f** was not recovered.

^{1}H NMR (DMSO-d_6) of **3a** δ=1 .70 (t, 1H, NH), 2.55 (s, 3H, CH_3), 4.17 (d, 2H, CH_2), 5.79 (s, 1H, HC=), 7.32—7.49 (m, 3H, 3′, 4′, 5′-H), and 7.87—7.91 (m, 2H, 2′, 6′-H); ^{13}C NMR (DMSO-d_6) of **3a** δ=13.79 (CH_3), 44.86 (CH_2), 86.50 (CH=), 126.75 (4′-C), 128.20 (3′, 5′-C), 130.58 (2′, 6′-C), 139.94 (1′-C), 168.62 (=CS(N)), 169.94 (COOH), and 183.88 (C=O).

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