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Stepwise Oxidation of Ketene Dithioacetal

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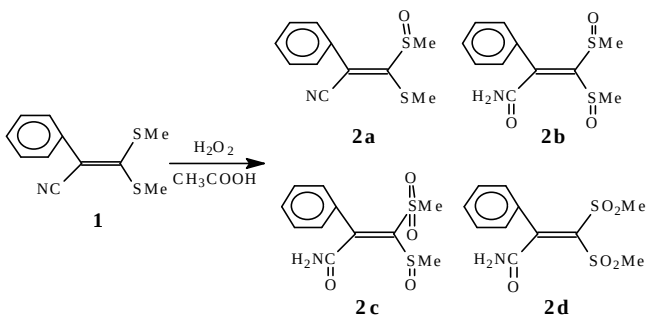
Abstract: Stepwise oxidation of ketene dithioacetal is found and the different oxidation products changed with the amount of oxidant, temperature and reaction time.

Keywords: Oxidation reaction,ketene dithioacetal,hydrogen peroxide.

Ketene dithioacetals[1-2] have demonstrated their potential for the synthesis of heterocycles, therefore, their synthesis and reactions have attracted much attention. The chemo- and stereo-selective conjugate addition of amine, organocuprate and Grignard reagent with ketene dithioacetal is well documented[3-5], and we chose to examine whether the conjugate addition of the phosphite to the ketene dithioacetal occurs to afford the corresponding phosphonyl/S-methyl α-cyano(oxo, ethoxycarbonyl *etc.*) ketene acetals[6]. During our study, we found that the conjugate addition of the phosphite to some ketene dithioacetal could not be easily effected. Therefore, we attempt to oxidize the ketene dithioacetal to the alkylsulfinyl or alkylsulfonyl ethylene for enhancing the electrophilic reactivity of the ketene dithioacetal using 30% hydrogen peroxide as oxidant. However, we surprisingly found that the oxidation of the ketene dithioacetal had regioselection between the two alkylthio group. To the best of our knowledge there are few examples[7] of the oxidation of the ketene dithioacetal, and the oxidant generally reacts on both alkylthio group. Here we firstly report the novel oxidation reaction of the ketene dithioacetal.

Scheme



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The α-cyano ketene dithioacetal **1** reacted with 30% hydrogen peroxide in the presence of glacial acetic acid to afford the different oxidation products (see **Scheme**).

The stepwise reaction led us to further study the effects of the amount of oxidant, temperature and reaction time. And our interest centered upon how to obtain the main oxidation product in different reaction conditions.

The oxidation reaction was monitored by HPLC. Firstly, we controlled the amount of hydrogen peroxide at 2 equiv., reaction temperature at 40°C, and changed the reaction time. The transformation ratio of different oxidation products is plotted against reaction time in **Figure 1**. After 8 h the transformation ratio of **2a** was 50% and any other products was not more than 20%. Compound **2a** was the main product. When the amount of oxidant was increased to 4 equiv., at 40°C for 8 h the reaction was different. The compound **2a** and **2b** was almost converted into **2c** and **2d** completely (see **Figure 2**). The results clearly indicated that the oxidation reaction firstly occurred on the one alkylthio group with increasing amount of hydrogen peroxide the alkylthio group was oxidized step by step to the alkylsulfinyl, then alkylsulfonyl group. In addition, with increasing amount of oxidant, the cyano group was transferred into the amide in the presence of glacial acetic acid.

Figure 1 Time course of the reaction in the presence of 2 equiv. H_2O_2 at 40℃

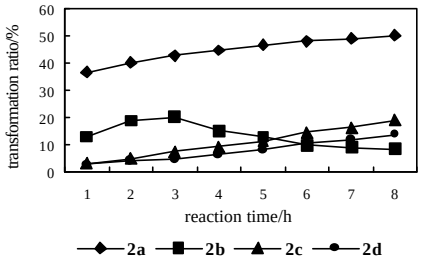
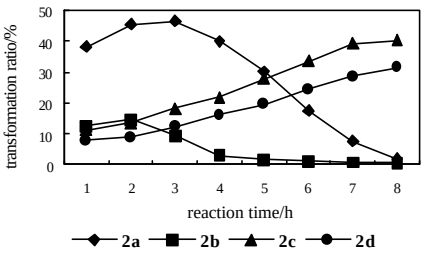


Figure 2 Time course of the reaction in the presence of 4 equiv. H_2O_2 at 40℃



We also investigated the effects of temperature and the amount of oxidant to the formation of **2a**. As dispicted in **Table 1** and **Table 2**, enhancing the temperature and the amount of oxidant, the transformation ratio of **2a** was decreased. It revealed that under this condition **2a** was converted into other oxidant products. Considering various factors we selected the different conditions to obtain the different main product.

The structures of oxidation products **2a~d** were confirmed by ^{1}H NMR, mass

spectroscopy and elemental analysis. In order to confirm the structure of **2a** and investigate its stereochemistry, a single crystal of the compound **2a** was analyzed by X-ray diffraction. The X-ray analysis (**Figure 3**) shows that the orientation of methylsulfinyl and phenyl is *cis* and confirms the E-stereochemistry of **2a**[8].

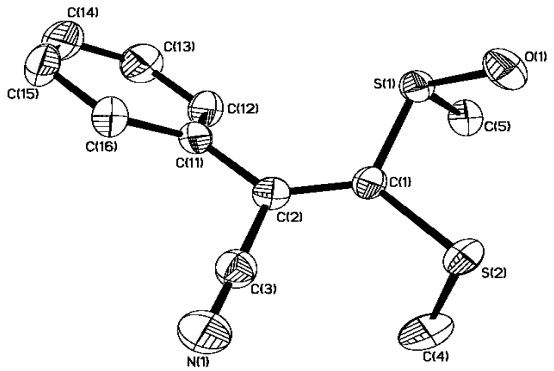
Table 1 Transformation ratio of oxidation product **2a** at different temperature in the presence of 2 equiv. H_2O_2 after 6 h

	reaction temperature/℃				
	40	60	80	100	116(reflux)
2a transformation ratio/%	48.0	45.6	43.2	41.0	35.1

Table 2 Transformation ratio of oxidation product **2a** using the different amount of oxidant at 40℃ after 6 h

	oxidant equiv.			
	1	2	4	6
2a transformation ratio/%	48.3	48.0	17.6	11.2

Figure 3 X-ray crystal structure of **2a**



In summary, we have reported the stepwise oxidation of ketene dithioacetal using cheap, safe oxidant-hydrogen peroxide. The applications of this method to other ketene dithioacetals and the connectivities with readily further transformation of the oxidant products to the conjugate addition with different nucleophiles are under way.

Experimental

Melting points were obtained on a Yanaco MP-500 apparatus without correction. ^{1}H NMR spectra were taken on a Bruker AC-P200 spectrometer using TMS as internal standard and elemental analysis was performed on a Yanaco MT-3 instrument. IR spectra were recorded on a Shimadzu-435 spectrometer.

The HPLC analysis was carried out using HP1090 Liquid Chromatograph. The column temperature was kept constant at 20°C. The analytes were eluted by a mixture of petroleum ether, isopropanol and methanol (6:2:1 by volume) at 1 mL min^{-1} flow rate,

and detected by UV absorption at 230 nm.

*Procedure for synthesis of **2a~b***

1,1-bis-methylthio-2-cyano-2-phenylethylene **1** (2.5 mmol) was dissolved in glacial acetic acid (10 mL). Then hydrogen peroxide (30%, 0.51 mL; 2 equiv.) was added into the mixture dropwise. Stirred at 40°C for 8 h, the reaction mixture was poured into water (20 mL). After extraction several times with ethyl acetate, the organic phase was washed with water, dried with anhydrous $MgSO_4$. After evaporation, the residue was purified by column chromatography on a silica gel using petroleum ether (60~90°C): ethyl acetate (3:1, V/V) as the eluent, giving the pale yellow solid **2a**.

Compound **2b** was prepared in the same method as **2a**, but using petroleum ether (60~90°C): ethyl acetate (1:1, V/V) as the eluent.

2a Yield 65%, mp 90~91°C. IR (KBr) ν: 2211, 1623, 1591, 1442, 1033, 758, 697 cm^{-1}. ^1H NMR ($CDCl_3$, δ ppm): 2.71 (s, 3H, SCH_3), 2.81 (s, 3H, $SOCH_3$), 7.33~7.45 (m, 5H, C_6H_5). Anal. $C_{11}H_{11}NOS_2$. Calcd: C, 55.62; H, 4.63; N, 5.90. Found: C, 55.68; H, 4.41; N, 6.00.

2b Yield 30%, mp 208~210°C. IR (KBr) ν: 3348, 3139, 1677, 1592, 1441, 1049, 779 cm^{-1}. ^1H NMR (d_6-DMSO, δ ppm): 3.35 (s, 3H, $SOCH_3$), 3.36 (s, 3H, $SOCH_3$), 7.27~8.06 (m, 5H, C_6H_5). Anal. $C_{11}H_{13}NO_3S_2$. Calcd: C, 48.71; H, 4.80; N, 5.17. Found: C, 48.29; H, 4.78; N, 4.87.

Procedure for synthesis of **2c~d** was the same as **2a**, only hydrogen peroxide was 2 equiv. more. The eluent for column chromatography was petroleum ether (60~90°C): ethyl acetate (1:1, V/V).

2c Yield 50%, mp 217~219°C. IR (KBr) ν: 3387, 3150, 1667, 1554, 1442, 1319, 1138, 1030, 775 cm^{-1}. ^1H NMR (d_6-DMSO, δ ppm): 3.16 (s, 3H, $SOCH_3$), 3.34 (s, 3H, SO_2CH_3), 7.39~7.50 (m, 5H, C_6H_5). Anal. $C_{11}H_{13}NO_4S_2$. Calcd: C, 45.99; H, 4.53; N, 4.88. Found: C, 46.00; H, 4.47; N, 4.80.

2d Yield 46%, mp 272~273°C. IR (KBr) ν: 3403, 3186, 1670, 1554, 1430, 1325, 1136, 1011, 769 cm^{-1}. ^1H NMR (d_6-DMSO, δ ppm): 3.29 (s, 3H, SO_2CH_3), 3.39 (s, 3H, SO_2CH_3), 7.43 (s, 5H, C_6H_5). Anal. $C_{11}H_{13}NO_5S_2$. Calcd: C, 43.56; H, 4.29; N, 4.62. Found: C, 43.38; H, 4.18; N, 4.40.

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