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H_2O_2 Assisted Oxidation of 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3, 2-*a*]-pyrimidine-6-carbonitrile

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Abstract:

Stepwise oxidation of 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3, 2-*a*]-pyrimidine-6-carbonitrile is found and the different oxidation products changed with the amount of oxidant, temperature and reaction time.

Keywords:

Oxidation reaction, 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile, hydrogen peroxide.

Introduction:

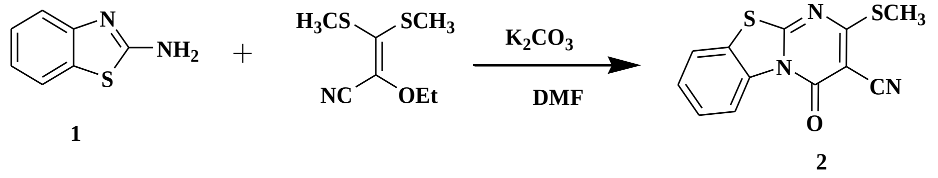
The derivatives of ketene dithioacetals[1-2] have demonstrated their potential for the synthesis of heterocycles; therefore, their synthesis and reactions have attracted much attention. The chemo- and stereo-selective conjugate addition of amine, organocuprate and grignard reagent with ketene dithioacetal is well documented [3-5], Therefore, we attempt to oxidize the 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile to the alkylsulfinyl or alkylsulfonyl ethylene for enhancing the electrophilic reactivity using 30% hydrogen peroxide as oxidant.

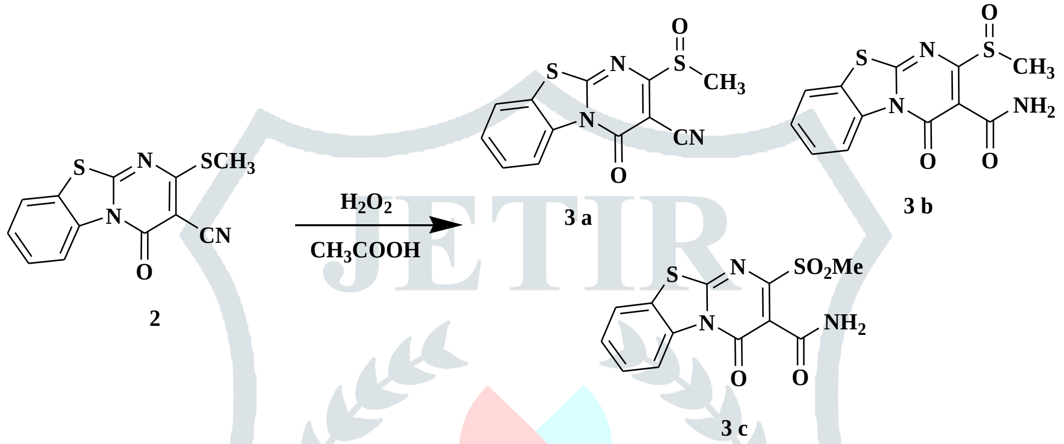
However, we surprisingly found that the oxidation of the 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3, 2-*a*]-pyrimidine-6-carbonitrile had regioselection of alkylthio group. To the best of our knowledge there are few examples 7 of the oxidation of the ketene dithioacetal, and the oxidant generally reacts on alkylthio groups. Here we firstly report the novel oxidation reaction of the 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile.

The oxidation of 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile plays an important role in organic synthesis while the development of new oxidative processes continues drawing attention in spite of the availability of numerous oxidizing reagents[6]. Such oxidizing reagents often used in stoichiometric amounts are often hazardous or toxic. Hence, in terms of economical and environmental concern, catalytic oxidation processes with inexpensive and environmental oxidants are extremely valuable. One favourite oxidant to resort to is hydrogen peroxide due to its environmental impact, since water is the only by product of such oxidative reactions[7].

The 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile **2** reacted with 30% hydrogen peroxide in the presence of glacial acetic acid to afford the different oxidation products (see **Scheme 2**). 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 **3a** was 50% and any other products was not more than 20%. Compound **3a** 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 **3a** and **3b** was almost converted into **3c** completely (see **Figure 2**). The results clearly indicated that the oxidation reaction firstly occurred on the 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.

Scheme 1 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3,2-*a*]-pyrimidine-6-carbonitrile **2**





Scheme 2 synthesis of 3a~c

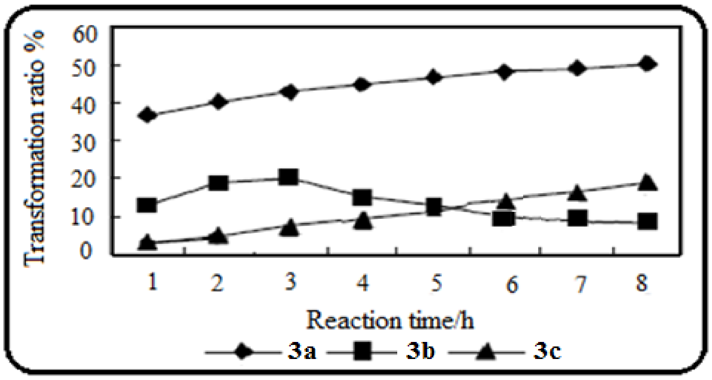


Figure 1 Time course of the reaction in the presence of **2** equiv. H_2O_2

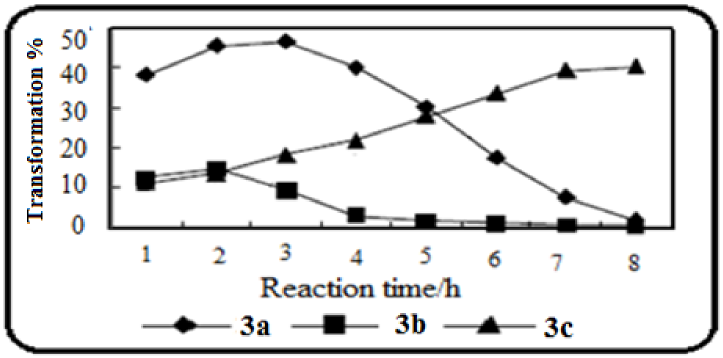


Figure 2 Time course of the reaction in the presence of **4** equiv. H_2O_2 at 40 ^{O}C

We also investigated the effects of temperature and the amount of oxidant to the formation of **3a**. As dispicted in **Table 1** and **Table 2**, enhancing the temperature and the amount of oxidant, the transformation ratio of **3a** was decreased. It revealed that under this condition **3a** 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 **3a~c** were confirmed by ^{1}H NMR, mass spectroscopy and elemental analysis.

Table 1 Transformation ratio of oxidation product 3a at different temperature in the presence of 2 equiv. H_2O_2 after 6 h

Reaction Temperature °C	40	60	80	100 (reflux)
3a Transformation ratio %	48.0	45.6	43.2	41.0

Table 2 Transformation ratio of oxidation product 3a using the different amount of oxidant at 40 °C after 6 h

Oxidant equivalent	1	2	4	6
3a Transformation ratio %	48.3	48.0	17.6	11.2

Experimental:

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on Win-Bommen B-104 IR Spectrophotometer with KBr pellets. 1H-NMR spectra was recorded on Bruker a VIII 500 MHz NMR Facility using DMSO-d6 as solvent. The chemical shifts are reported as parts per million downfield from tetramethyl silane (Me_4Si). The HPLC analysis was carried out using HP1090 Liquid Chromatography. 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.

Procedure for synthesis of 7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3, 2-*a*]-pyrimidine-6-carbonitrile [2]

A mixture of 2-amino benzothiazole (0.001 moles) and ethyl-2-cyano-3, 3-bis, methyl acrylate (0.001 moles) was dissolved in N, N-dimethyl formamide (DMF). A pinch of anhydrous K_2CO_3 was added and the reaction mixture refluxed for 4 hours. The completion of reaction was checked by TLC. After completion of the reaction, the contents were cooled at room temperature and poured into ice-cold water. The separated solid product thus obtained filtered and washed with water. The crude product was recrystallised by using DMF-ethanol.

[2] Yield 65%, mp 195~197°C. IR (KBr) *V*: 2211, 1623, 1591, 1442, 1033, 758, 697 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ ppm): 2.41 (s, 3H, SCH_3), 7.19~7.45(m, 4H), Anal. $C_{12}H_7N_3OS_2$. Calcd: C, 52.73; H, 2.60; N, 15.40; O, 5.89; S.23.56, Found: C, 52.72; H, 2.58; N, 15.37; O, 5.85; S.23.46.

Procedure for synthesis of 3a~b:

7-methyl sulfanyl-5-oxo-5*H*-benzothiazolo-[3, 2-*a*]-pyrimidine-6-carbonitrile **2** (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 **3a**. Compound **3b** was prepared in the same method as **3a**, but using petroleum ether (60~90°C): ethyl acetate (1:1, V/V) as the eluent.

Procedure for synthesis of **3c** was the same as **3a**; only hydrogen peroxide was 2 equiv. more. The eluent for column chromatography was petroleum ether (60~90°C): ethyl acetate (1:1, V/V).

[3a] Yield 65%, mp 225~227°C., IR (KBr) *V*: 3281, 2211, 1623, 1591, 1442, 1033, 758, 697 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ ppm): 2.86 (s, 3H, SOCH$_3$), 7.19~7.45(m, 4H), Anal. $C_{12}H_7N_3O_2S_2$. Calcd: C, 49.81; H, 2.44; N, 14.52; O, 11.05; S.22.16, Found: C, 49.83; H, 2.48; N, 14.83; O, 11.10; S.22.19.

[3b] Yield 65%, mp 240~242°C., IR (KBr) *V*: 3281, 2211, 1623, 1591, 1442, 1033, 758, 697 cm^{-1}. ^{1}H NMR (CDCl$_3$, δ ppm): 3.21 (s, 3H, SOCH$_3$), 6.03 (s, 2H, NH$_2$), 7.66~7.75(m, 4H), Anal. $C_{12}H_9N_3O_3S_2$. Calcd: C, 46.82; H, 2.99; N, 13.69; O, 15.68; S.20, Found: 88C, 46.81; H, 2.94; N, 13.67; O, 15.62; S.20.86.

[3c] Yield 65%, mp 275~278°C., IR (KBr) *V*: 3403, 3186, 1623, 1591, 1442, 1033, 758, 697 cm^{-1}. ^{1}H NMR (d$_6$-DMSO, δ ppm): 3.29 (s, 3H, SO$_2$CH$_3$), 6.03 (s, 2H, NH$_2$), 7.88~7.95(m, 4H), Anal. $C_{12}H_9N_3O_4S_2$. Calcd: C, 44.59; H, 2.84; N, 13.03; O, 19.80; S.19.85, Found: C, 44.57; H, 2.81; N, 13.00; O, 19.79; S.19.83.

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.

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