Silver Ion-Mediated Desulfurization of *N,N*-Disubstituted Dithiocarbamate Derivatives

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Abstract : Silver ion-mediated desulfurization of *N*-aroyl-*S*-(disubstituted thiocarbamoyl)-thiohydroxylamines (**1**) and disubstituted dithiocarbamic acid phenacyl esters (**4**) in aqueous solution gives the corresponding their carbamoyl derivatives. On the other hand, the reaction of **4** in acetic acid leads to formation of 2-(*N,N*-disubstituted amino)-5-phenyl-1,3-oxathiolium salts in one pot.

Key words : desulfurization, silver salt, *N*-aroyl-*S*-(disubstituted thiocarbamoyl)-thiohydroxylamine, disubstituted dithiocarbamic acid phenacyl ester, 1,3-oxathiolium salt

1 Introduction

During our serial studies on synthesizing 1,4,2-dithiazolium salts and their reactivity toward various kinds of nucleophiles¹⁾, we have newly developed the convenient synthetic route by using *S*-thiocarbamoyl thiohydroxylamines leading to their *N*-aroyl derivatives (**1**)²⁾. Through tests for the functionality of **1** including the related compounds, we found that several derivatives of **1** have excellent anti-fogging ability for silver halide photography, and some of them exhibit the performance superior to conventional antifoggants having heterocyclic thiol structure³⁾. This fact suggested that there is a strong interaction between **1** and silver ion. We paid much attention to this fact and researched on desulfurization of **1** and the *carba*-analogs, *N,N*-disubstituted dithiocarbamic acid phenacyl esters (**4**), by a silver salt. Meanwhile, many studies on conversion of thiocarbamoyl compounds into the corresponding carbamoyl ones by using various kinds of reagents have been reported^{4)~9)}. However, there is few study on desulfurization of them by using a silver salt.

2 Results and Discussion

The title reaction of **1** was examined at first. When a mixture of *N*-(4-chlorobenzoyl)-*S*-(dimethylthiocarbamoyl)thiohydroxylamine (**1a**) in chloroform and aqueous silver nitrate solution was stirred at room temperature, **2a** (57% yield) and a small amount of **3a** (18%) were obtained together with silver sulfide. On the other hand, the minor products **3a** were identified by direct comparison with the authentic sample¹⁰⁾. Similarly, *N*-(4-methoxybenzoyl)-*S*-(dimethylthiocarbamoyl)thiohydroxylamine (**1b**) and *N*-benzoyl-*S*-(dimethylthiocarbamoyl)thiohydroxylamine (**1c**) afforded the corresponding *S*-dimethylcarbamoylthiohydroxylamine **2b** (55%), 1,3,4-oxathiazol-2-one **3b** (23%), and **2c** (68%), **3c** (20%), respectively. Treatment of *N*-benzoyl-*S*-thiobenzoylthiohydroxylamine (**1d**)¹¹⁾ with aqueous silver nitrate solution gave *N,S*-dibenzoylthiohydroxylamine (**2d**) alone which is alternatively given by benzoylation of *S*-benzoylthiohydroxylamine¹²⁾.

A plausible mechanism affording to 2 and 3 from 1 is shown in **Scheme 1**. Silver ion attacks the thiocarbamoyl sulfur atom; the thiocarbamoyl carbon is donated by the lone pair electron of the amido oxygen, and then the attack of another silver ion to the sulfur atom affords 1,3,4-oxathiazolium cation (**A**) as an intermediate with eliminating silver sulfide. **A** is immediately subject to attack of OH⁻ at the 2-position to give simultaneously 2 and 3 competitively with eliminating dimethylamine.

Scheme 1

N,N-Disubstituted dithiocarbamic acid phenacyl esters (**4**), known to be precursors of 1,3-dithiolium salts¹³, exhibited only poor anti-fogging ability through the functionality test³. Therefore, their desulfurization by silver salts needed a little severe conditions than that of **1**. Under refluxing with silver salt in aqueous methanol, morpholine dithiocarboxylic acid phenacyl ester (**4a**) gave morpholine thiocarboxylic acid *S*-phenacyl ester (**5a**) together with silver sulfide. In the conventional way, compound **5a**, known to be the precursor of 1,3-oxathiolium salts (**6**), has been prepared through esterification of *N,N*-disubstituted thiocarbamates, given by secondary amines and poisonous carbonyl sulfide¹⁴. On the contrary, 2-morpholino-5-phenyl-1,3-oxathiolium salt (**6a**) was directly obtained when **4a** was refluxed with silver salt in acetic acid. Through the treatment with silver salt, other dithiocarbamic acid phenacyl esters (**4b-e**) gave also respective 1,3-oxathiolium salts (**6b-e**) conveniently in good yields. The pathway to **5** from **4** is considered to be the same mechanism forming **2**, and **6a-e** could be isolated as stable salts in acetic acid though they were considered to be corresponding to the intermediate **A** in **Scheme 1**. The pathway to **5,6**, and the 1,3-dithiolium salts from **4** is thus summarized in **Scheme 2**.

3 Experimental

Melting points were determined by a Mettler FP82 apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer using KBr disks. Mass spectra were measured with a Shimadzu GCMS-QP2000A mass spectrometer. ¹H NMR spectra were recorded on a Varian Gemini 300BB spectrometer using TMS as an internal standard.

General procedure for treatment of *N*-aroyl-*S*-(disubstituted thiocarbamoyl) thiohydroxylamines (1a-1c**) with aqueous silver nitrate.**

A chloroform solution (10 ml) of **1** (2 mmol) and an aqueous solution (10 ml) of silver nitrate (820 mg, 4.8 mmol) were mixed and stirred vigorously for 5h at room temperature.

Scheme 2

The resulting organic layer was passed through on a silica gel column (Merck silica gel 60, hexane:AcOEt=2:1), two products, 2 and 3, were fractionated, and then purified by recrystallization (2: methanol, 3: hexane). The characterization data of 2a-c are shown below, and the structures of 3a-c were confirmed by direct comparison with authentic samples, respectively, to be 5-(4'-chlorophenyl)-1,3,4-oxathiazol-2-one (3a), 76 mg (18%), mp 129–130°C (127–130°C¹⁰); 5-(4'-methoxyphenyl)-1,3,4-oxathiazol-2-one (3b), 96 mg (23%), mp 111–112°C (112°C¹⁵); 5-phenyl-1,3,4-oxathiazol-2-one (3c), 84 mg (20%), mp 69–70°C (68.5–70°C¹⁰).

***N*-(4-Chlorobenzoyl)-*S*-dimethylcarbamoylthiohydroxylamine (2a).**

Colorless powder; yield 57%; mp 146°C; ¹H NMR (CDCl₃) δ=3.00 (6H, s), 7.2–7.83 (5H, m); ¹³C NMR (CDCl₃) δ=35.38, 37.07, 128.67, 129.36, 130.97, 138.58, 167.99, 168.08; MS *m/z* 258 (M⁺), 139 (ClC₆H₄CO⁺), 72 ([CH₃]₂NCO⁺); IR 3192 (NH), 1675 (C=O), 1652 (C=O), 1241, 1093 cm⁻¹. Anal. Found: C, 46.54; H, 4.10; N, 10.80%. Calcd for C₁₀H₁₁N₂O₂SCl: C, 46.42; H, 4.29; N, 10.83%.

***N*-(4-Methoxybenzoyl)-*S*-dimethylcarbamoylthiohydroxylamine (2b).**

Colorless powder; yield 55%, mp 173°C; ¹H NMR (CDCl₃) δ=3.00 (6H, s), 3.80 (3H, s), 6.73–7.92 (5H, m); ¹³C NMR δ=36.97, 55.30, 113.72, 125.30, 129.90, 162.84, 167.93, 168.59; MS *m/z*; 254 (M⁺), 135 (CH₃OC₆H₄CO⁺), 72 ([CH₃]₂NCO⁺); IR 3308, 1668 (C=O), 1646 (C=O), 1247, 1089 cm⁻¹. Anal. Found: C, 52.07; H, 5.52; N, 11.13%. Calcd for C₁₁H₁₄N₂O₃S: C, 51.95; H, 5.55; N, 11.02%.

***N*-Benzoyl-*S*-dimethylcarbamoylthiohydroxylamine (2c).**

Colorless granules; yield 68%; mp 118°C; ¹H NMR (CDCl₃) δ=2.98 (6H, s), 7.26–7.29 (6H, m); ¹³C NMR δ=35.25, 36.95, 127.84, 128.54, 132.21, 133.04, 167.55, 169.27; MS *m/z*; 224 (M⁺), 105 (PhCO⁺), 72 ([CH₃]₂NCO⁺); IR 3228 (NH), 1682 (C=O), 1640 (C=O), 1246, 1103 cm⁻¹. Anal. Found: C, 53.60; H, 5.67; N, 12.39%. Calcd for C₁₀H₁₂N₂O₂S: C, 53.55; H, 5.39; N, 12.49%.

Conversion of *N*-benzoyl-*S*-thiobenzoylthiohydroxylamine¹¹⁾ (1d) into *N,S*-dibenzoylthiohydroxylamine¹²⁾ (2d).

To a chloroform solution (5 ml) of 1d (273 mg, 1 mmol) was treated with aqueous solution of silver nitrate (410 mg, 2.4 mmol) in the same procedure as the above, and the mp and IR spectra of 2d (200 mg, 78%) were completely agreed with the authentic data¹¹⁾.

Conversion of morpholine dithiocarboxylic acid phenacyl ester (4a) into morpholine thio-carboxylic acid phenacyl ester (5a).

To an aqueous methanol solution (methanol 4 ml, water 1 ml) of morpholine dithiocarboxylic acid phenacyl ester (281 mg, 1 mmol) was added silver trifluoroacetate (453 mg, 2.05 mmol) and refluxed for 2h. After removal of silver sulfide, the filtrate was poured into water (20 ml). The resulting crude product was extracted with dichloromethane, and recrystallized from isopropyl ether to give 5a; 153 mg (60%); mp 81°C (80–81°C¹³⁾)

Conversion of 4a into 2-morpholino-5-phenyl-1,3-oxathiolium salts (6a).

To an acetic acid solution (5 ml) of **4a** (281 mg, 1 mmol) silver perchlorate (440 mg, 2.1 mmol) was added and the mixture was refluxed for 2h. After removing silver sulfide, the filtrate was poured into ether, and the resulting precipitate was recrystallized from methanol to give **6a**. According to the above-mentioned method, 1,3-oxathiolium salts (**6b-e**) were also obtained. Their characterization data are shown below.

Colorless prisms; yield 180 mg (52%); mp 173°C; ^1H NMR (DMSO- d_6) δ =3.76(*m*, 4H), 4.09 (*m*, 4H), 7.42–7.93 (*m*, 6H); ^{13}C NMR δ =42.88, 63.31, 100.16, 124.46, 127.60, 129.24, 129.74, 151.67, 171.17; IR 3104, 1644, 1274, 1075 cm^{-1} . Anal. Found: C, 44.65; H, 4.11; N, 4.09%. Calcd for $\text{C}_{13}\text{H}_{14}\text{NSClO}_6$: C, 44.90; H, 4.06; N, 4.03%.

2-Piperidino-5-phenyl-1,3-oxathiolium perchlorate (6b).

Colorless plates; yield 231 mg (67%); mp 176°C (lit. 175–177°C)¹³.

2-Diethylamino-5-(4'-bromophenyl)-1,3-oxathiolium tetrafluoroborate (6c).

Colorless prisms; yield 250 mg (63%); mp 195°C; ^1H NMR (DMSO- d_6) δ =1.34 (*t*, 6H, J =7.14 Hz), 3.74 (*q*, 2H, J =7.14 Hz), 3.94 (*q*, 2H, J =7.14 Hz), 7.76–7.85 (*m*, 4H), 7.89 (*s*, 1H); ^{13}C NMR δ =10.68, 11.94, 46.55, 49.58, 103.54, 125.34, 127.28, 131.79, 132.41, 150.23, 177.63; IR 3100, 1657, 1605, 1060 cm^{-1} . Anal. Found: C, 38.94; H, 3.69; N, 2.95%. Calcd for $\text{C}_{13}\text{H}_{15}\text{NSOBrBF}_4$: C, 39.03; H, 3.78; N, 3.50%.

2-Diethylamino-5-(4'-nitrophenyl)-1,3-oxathiolium perchlorate (6d).

Ivory powder; yield 150 mg (40%); mp 208°C; ^1H NMR (DMSO- d_6) δ =1.33 (*t*, 6H, J =7.42 Hz), 3.77 (*q*, 2H, J =7.42 Hz), 3.94 (*q*, 2H, J =7.42 Hz), 8.15–8.40 (*m*, 5H); ^{13}C NMR δ =10.70, 11.94, 46.66, 49.65, 107.50, 124.16, 124.59, 125.30, 126.53, 131.71, 151.70, 177.57; IR 3080, 1651, 1517, 1344, 1080 cm^{-1} . Anal. Found: C, 41.24; H, 3.82; N, 7.22%. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{SClO}_7$: C, 41.22; H, 3.99; N, 7.40%.

2-Diethylamino-5-phenyl-1,3-oxathiolium perchlorate (6e).

Colorless granules; yield 220 mg (65%); mp 133°C; ^1H NMR (DMSO- d_6) δ =1.35 (*t*, 6H, J =7.42 Hz), 3.74 (*q*, 2H, J =7.42 Hz), 3.95 (*q*, 2H, J =7.42 Hz), 7.55–7.88 (*m*, 6H); ^{13}C NMR δ =10.71, 11.96, 46.59, 49.62, 102.43, 125.31, 126.10, 129.42, 130.79, 151.26, 177.72; IR 3120, 2980, 1648, 1078 cm^{-1} . Anal. Found: C, 46.82; H, 4.65; N, 4.01%. Calcd for $\text{C}_{13}\text{H}_{16}\text{NSClO}_5$: C, 46.78; H, 4.83; N, 4.20%.

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日本油化学会誌本号掲載 論文要旨

〔総説〕 アポトーシスにおける脂質メディエーターの役割

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サイトカインによるアポトーシスの誘導においてアラキドン酸やセラミドという脂質メディエーターの重要性が指摘されている。TNF に抵抗性を示す亜株のうちには cPLA₂ 活性が欠如しているものがある。この細胞に cPLA₂ の cDNA を発現させると感受性が回復する。さらに親株の感受性細胞を TNF 処理するとセラミドの産生がおこるのに対し抵抗性株では起こらない。しかしこの抵抗性株をセラミドで処理するとアポトーシスが誘導される。これらの結果は二つの脂質メディエーターがアポトーシス誘導において重要な役割をはたしていることを示すとともに両者が互いに関連しあっていることを示唆している。本総説ではこれら脂質メディエーターのアポトーシスにおける役割を、他のメディエーターとの相互関係について留意しつつ、まとめてみたい。

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〔報文〕 *n*-3 系多価不飽和脂肪酸高含有 β -リゾリン脂質
によるヒト赤血球変形能の増進作用細川 雅史*¹・小野 雅代*¹・高橋是太郎*¹・井上 良計*²*¹ 北海道大学水産学部 (〒041-8611 函館市港町 3-1-1)*² 備前化成株式会社 (〒709-0716 岡山県赤磐郡熊山町)

リポザイム(ケカビ由来固定化酵素)を用いたドコサヘキサエン酸(DHA)強化鶏卵黄ホスファチジルコリン(PC)の選択的部分加水分解反応により、sn-2 位に DHA の結合したリゾホスファチジルコリン(β -DHA-LPC)を調製した。この β -DHA-LPC は、ヒト赤血球懸濁液に対し 5 μ M の濃度においても、速やかにヒト赤血球中に取り込まれ、その変形能を向上させることができることを人工毛細血管モデルにより明らかにした。

(連絡者：高橋是太郎) Vol. 47, No. 12, 1313 (1998)

〔報文〕 *N*, *N*-ジ置換ジチオカルバミン酸誘導体の銀イオンが介在する脱硫反応

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N-アロイル-*S*-(ジ置換チオカルバモイル)-チオヒドロキシルアミンおよび置換ジチオカルバミン酸のフェナシルエステル(4)を水の存在下で、標記の反応をさせたところ、*S*-*O*置換が起こり、対応するカルバモイル誘導体が得られた。一方 4 を酢酸中で銀塩と処理すると、2-(*N*, *N*-ジ置換アミノ)-5-フェニル-1, 3-オキサチオリウム塩が得られた。

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