SILVER(I) ION-MEDIATED DESULFURIZATION-CYCLIZATION OF ISOTHIOCYANATES WITH SEVERAL HYDROXY ACIDS AND *N*-SUBSTITUTED AMINO ACIDS

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Abstract - The title reaction of 2-hydroxy-2-methylpropionic acid with phenyl isothiocyanate gave 5,5-dimethyl-3-phenyl-2,4-oxazolidinedione. The structure was determined by X-Ray crystal analysis, and the reaction pathway was estimated. The reactions of other 2-hydroxyl acids with isothiocyanates also gave some 2,4-oxazolidinediones in good yields. 3-Hydroxybutyric acid, salicylic acid, 3-hydroxy-2-naphthoic acid, and 3-hydroxypyridine-2-carboxylic acid afforded the corresponding cyclic products through the desulfurization-cyclization with isothiocyanate, respectively. *N*-Substituted amino acids gave several imidazolidine-2,4-diones in the same way.

In the previous papers we reported that silver ion-mediated desulfurization-condensation of diaryl thioketones or carbon disulfide with reagents, such as hydroxyl compounds, amino and active methylene ones, gave various kinds of products with liberating silver sulfide under mild conditions.[1-4] Meanwhile, it has been known that isothiocyanates are versatile materials for synthesizing various heterocycles.[5] We anticipated that isothiocyanates would be activated by a silver salt as well as thioketones to afford various kinds of products through the desulfurization-condensation with some nucleophiles, and attempted to the title reaction of isothiocyanates with various hydroxy acids and *N*-substituted amino acids. We report here novel and convenient synthetic routes giving 2,4-oxazolidinedione, 1,3-oxazine-2,4-dione, and imidazolidine-

2,4-dione derivatives.

At first, we tried the reaction of phenyl isothiocyanate with 2-hydroxy-2-methylpropionic acid in the presence of silver trifluoroacetate and triethylamine in acetonitrile to give a desulfurization-condensation product (**1**) with liberating silver sulfide in an excellent yield. The molecular structure of **1** was unequivocally established by a single crystal X-Ray diffraction structure analysis.[6] An ORTEP drawing is given as shown in Figure 1, and **1** was identified to be 5,5-dimethyl-3-phenyl-2,4-oxazolidinedione. The oxazolidine ring was almost planar, and the angle between it and the phenyl group was 64.5 °.

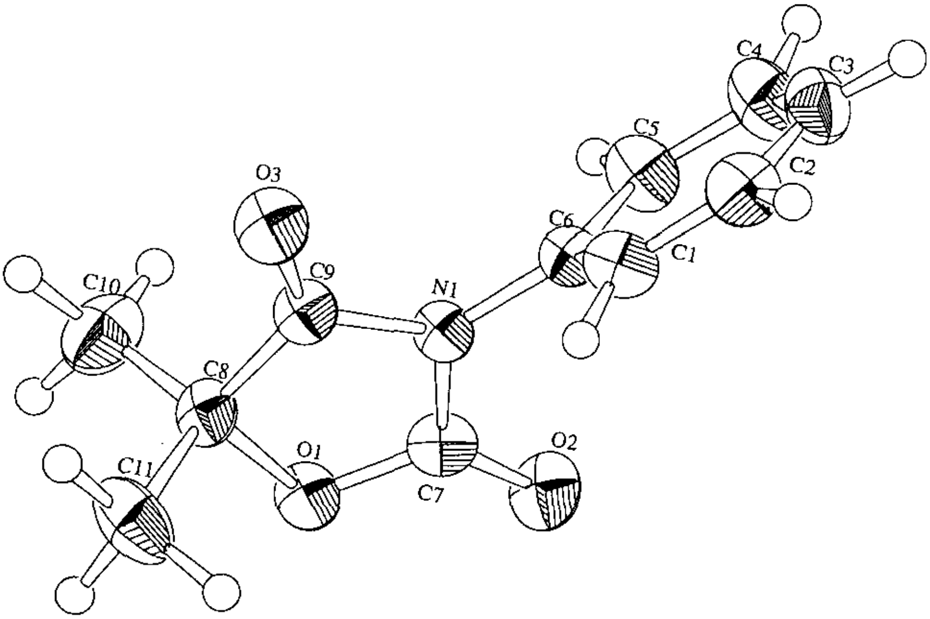
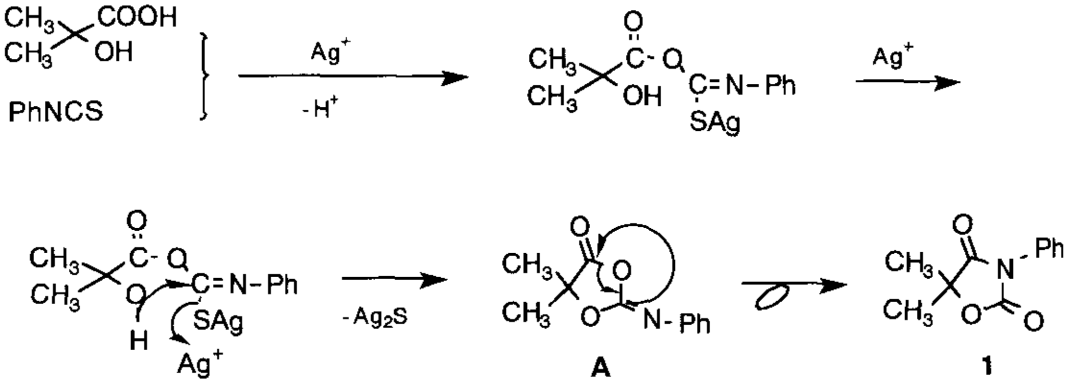


Figure 1 ORTEP drawing of the molecular structure of **1** as 50 % probability ellipsoids.

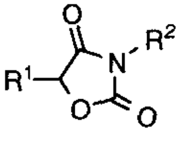
Selected bond length (Å) : O1-C7 1.334(4), O1-C8 1.469(4), C8-C9 1.508(5), O3-C9 1.209(4), N1-C9 1.390(4), N1-C7 1.397(4), N1-C6 1.419(4), O2-C7 1.204(4).

Selected bond angles (°) : C6-N1-C7 123.5(2), C6-N1-C9 125.8(2), C7-N1-C9 110.6(2), N1-C9-O3 126.5(2), C8-C9-O3 127.6(3), C9-C8-C11 111.0(3), C11-C8-C10 114.7(3), O1-C8-C10 108.5(3), C8-O1-C7 110.4(2), O2-C7-O1 124.4(3), N1-C7-O2 126.1(3), O1-C7-N1 109.5(2).

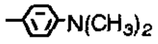
A plausible mechanism affording **1** was shown in Scheme 1. In the presence of excess triethylamine and a silver salt, 2-hydroxy-2-methylpropionate anion would add to phenyl isothiocyanate, and the resulting adduct would afford condensation product (**A**) through the desulfurization by silver ion as an intermediate to convert into **1** immediately by an intramolecular O to N acyl migration. This migration is considered to be the same that occurs in the reaction of carbodiimides or ketenimines with carboxylic acids to afford acylureas[7] or imides,[8] respectively. Similarly, the desulfurization-condensations of other 2-hydroxy carboxylic acids with isothiocyanates gave also 3,5-disubstituted 2,4-oxazolidinediones (**2** - **5**) in good yields.



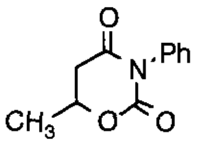
Scheme 1



2 - 5

	-R^1	-R^2
2 :	-CH_3	-Ph
3 :	-CH_3	
4 :	-CH_3	
5 :	-$(CH_2)_{13}CH_3$	-Ph

This desulfurization-condensation could be applied to β-hydroxy acids, such as 3-hydroxybutyric acid, salicylic acid, 3-hydroxy-2-naphthoic acid, and 2-hydroxypyridine-3-carboxylic acid, in the same manner to afford 6-methyl-3-phenyl-5,6-dihydro-1,3-oxazine-2,4(3*H*)-dione (**6**), 3-substituted benzo-1,3-oxazine-2,4(3*H*)-diones (**7**, **8**), 3-allylnaphtho-1,3-oxazine-2,4(3*H*)-dione (**9**), and 3-phenylpyridino-1,3-oxazine-2,4(3*H*)-dione (**10**), respectively.



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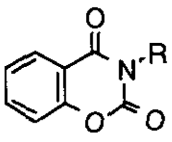
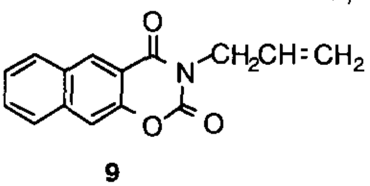


7, 8

7: R = Ph
8: R = CH_2Ph



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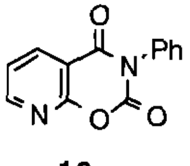

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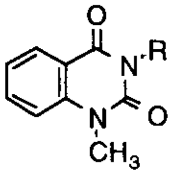
On the other hand, the reaction was applied to γ-hydroxy acids, such as 4-hydroxybutyric acid, 2-hydroxymethylbenzoic acid, and 2-hydroxyphenylacetic acid, but seven-membered ring products expected were not obtained.

We subsequently examined the reaction of phenyl isothiocyanate with some *N*-monosubstituted amino acids in the presence of silver trifluoroacetate and triethylamine in the same way, and *N*-methylanthranilic acid, *N*-phenylglycine, *N*-acetylglycine, and indole-2-carboxylic acid gave also respective desulfurization-cyclization products (**11**, **12**, **13**, and **14**) in good yields.



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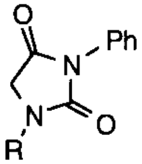
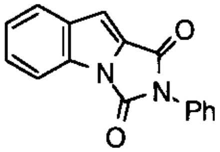


12 : R = Ph
13 : R = COCH3

12 , **13**



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In conclusion, we found that isothiocyanates, as well as carbon disulfide and diaryl thioketones, were activated by a silver ion, and that 2,4-oxazolinedione, 1,3-oxazine-2,4-dione, quinazoline-2,4-dione, and imidazoline-2,4-dione derivatives were conveniently synthesized in good yields through the desulfurization-cyclization with α- or β-hydroxy acids or *N*-substituted amino acids, respectively.

EXPERIMENTAL

All melting points were measured on a Mettler FP90 microscope plate, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300BB spectrometer in the solution of $CDCl_3$ using TMS as an internal standard. IR spectra were measured on a JASCO (FT-5300) spectrophotometer using KBr disks.

General procedure for synthesizing 1 - 14.

To a mixture of a hydroxy acid or an *N*-substituted amino acid (1.2 mmol), an isothiocyanate (1.0 mmol) and silver trifluoroacetate (530 mg, 2.4 mmol) in acetonitrile (5 mL) was added triethylamine (360 mg, 3.6 mmol) with stirring, and the reaction mixture was heated to reflux for 1 h. After removal of silver sulfide by filtration and evaporation of the solvent under reduced pressure, the resulting residue was washed with water, recrystallized from an appropriate solvent to give the respective heterocyclic product (**1-14**). The solvent, yield, mp, and the characterization data are shown below.

5,5-dimethyl-3-phenyl-2,4-oxazolidinedione (1).

Methanol; colorless granulars; yield (195 mg, 95 %); mp 108 °C. ^1H NMR δ = 1.69 (6H, *s*), 7.42 - 7.49 (5H, *m*); ^{13}C NMR δ = 23.79, 83.39, 125.53, 128.82, 129.30, 131.01, 153.29 (C=O), 174.87(C=O); ms *m/z* 205 (M^+); IR ν 1819 (C=O), 1742 (C=O), 1423, 1286, 1236, 1176 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.41; H, 5.39; N, 6.76.

5-Methyl-3-phenyl-2,4-oxazolidinedione (**2**).

Ethanol; colorless needles; yield 150 mg (79 %); mp 142 °C (lit.,[9] 141-142 °C).

5-Methyl-3-(4'-chlorophenyl)-2,4-oxazolidinedione (**3**).

Ethanol; colorless plates; yield 207 mg (92 %); mp 177 °C (lit., [10] 177-178 °C).

5-Methyl-3-(4'-dimethylaminophenyl)-2,4-oxazolidinedione (***4***).

Methanol; colorless needles; yield 206 mg (88 %); mp 127 °C. ^1H NMR δ = 1.68 (3H, *d*, *J* = 6.9 Hz), 2.98 (6H, *s*), 4.98 (1H, *q*, *J* = 6.9 Hz), 6.72 - 6.77 (2H, *m*), 7.18 - 7.26 (2H, *m*); ^{13}C NMR δ = 16.68, 40.29, 75.79, 112.36, 118.96, 126.59, 150.72, 154.78 (C=O), 173.11(C=O); MS *m/z* 234 (M^+), 162; IR ν 1811 (C=O), 1734 (C=O), 1525, 1420, 1184 cm^{-1}. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.45; H, 6.02; N, 12.11.

5-Tetradecyl-3-phenyl-2,4-oxazolinedione (**5**).

Hexane; colorless powder; yield 302 mg (81 %); mp 77 °C. ^1H NMR δ = 0.88 (3H, *t*, *J* = 7.2 Hz), 1.26 - 2.10 (26H, *m*), 4.94 (1H, *m*), 7.43 - 7.48 (5H, *m*); ^{13}C NMR δ = 13.99, 22.57, 23.95, 28.87, 29.15, 29.25, 29.35, 29.46, 29.52, 29.55, 29.58, 31.01, 31.82, 79.50, 125.60, 128.98, 129.43, 130.88, 154.29 (C=O), 172.08 (C=O); MS *m/z* 373 (M^+), 119; IR ν 2918, 1819 (C=O), 1745 (C=O), 1510, 1431, 1188 cm^{-1}. Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 73.98; H, 9.50; N, 3.69.

6-Methyl-3-phenyl-5,6-dihydro-1,3-oxazine-2,4(*3H*)-dione (**6**).

Ethanol; colorless powder; yield 146 mg (71 %); mp 174 °C. ^1H NMR δ = 1.55 (3H, *m*), 2.80 - 2.92 (2H, *m*), 4.80 (1H, *m*), 7.19 (2H, *m*), 7.42 - 7.50 (3H, *m*); ^{13}C NMR δ = 20.18 (CH_3), 38.47, 70.99, 128.26, 128.99, 129.37, 134.62, 151.31 (C=O), 167.96 (C=O); MS m/z 205 (M^+), 119, 91; IR ν 1763 (C=O), 1709 (C=O), 1402, 1356, 1249 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.58; H, 5.40; N, 6.97.

3-Phenyl-1,3-benzoxazine-2,4(*3H*)-dione (**7**).

Ethanol; colorless powder; yield 222 mg (93 %); mp 245 °C (lit.,[11] 244 °C).

3-Benzyl-1,3-benzoxazine-2,4(*3H*)-dione (**8**).

Ethanol; colorless powder; yield 233 mg (92 %); mp 134 °C (lit.,[12] 133 - 134 °C).

3-Allyl-1,3-naphthoxazine-2,4(*3H*)-dione (9).

Acetonitrile; colorless powder; yield 109 mg (43 %); mp 189 °C. ^{1}H NMR δ = 4.67 - 4.71 (2H, *m*), 5.27 - 5.43 (2H, *m*), 5.92 - 6.05 (1H, *m*), 7.52 - 8.69 (6H, *m*); ^{13}C NMR δ = 44.58, 112.58, 113.38, 119.20, 126.60, 127.59, 129.66, 130.02, 130.24, 130.52, 130.84, 137.07, 147.97, 160.57; MS *m/z* 253 (M^+), 170; IR ν 1747, 1684, 1635, 1467, 1383, 1342, 1242 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.30; H, 4.40; N, 5.25.

3-Phenyl-1,3-pyridinoxazine-2,4(*3H*)-dione (10).

Ethyl acetate; colorless powder; yield 106 mg (44 %); mp 234 °C. ^{1}H NMR δ = 7.45 - 7.59 (6H, *m*), 8.50 - 8.54 (1H, *m*), 8.73 - 8.76 (1H, *m*); ^{13}C NMR δ = 109.85, 122.44, 128.01, 129.68, 129.77, 133.84, 138.98, 147.10, 155.47, 158.21, 160.03; MS *m/z* 240 (M^+), 119 ($[PhNCO]^+$); IR ν 1773, 1703, 1585, 1437, 1371, 1298 cm^{-1}. Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.06; H, 3.33; N, 11.63.

1-Methyl-3-phenyl-2,4-quinazolidinedione (11).

Ethanol; colorless powder; yield 214 mg (85 %); mp 230 °C (lit.,[13] 229 - 230 °C).

1,3-Diphenyl-2,4-imidazolidinedione (12).

Ethanol; colorless plates; yield 161 mg (64 %); mp 139 °C (lit.,[14] 139 °C).

1-Acetyl-3-phenyl-2,4-imidazolidinedione (13).

Ethanol; colorless powder; yield 126 mg (58 %); mp 177 °C (lit.,[15] 177 - 178 °C).

2-Phenylimidazolo[*1,5-a*]indole-1,3-dione (14).

Acetonitrle; colorless powder; yield 225 mg (85 %); mp 212 °C (lit.,[16] 212 - 213 °C).

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6. X-Ray crystallographic analysis of compound (**1**).

A needle-like crystal of having approximate dimension of 0.6 x 0.1 x 0.1 mm was used. X-Ray data were collected on an Enraf-Nonius CAD4 diffractometer by using graphite-monochromatized CuKα radiation (λ =

1.5418 Å). Crystal data : $C_{11}H_{11}NO_3$, monoclinic, space group $P2_1/a$, a = 5.563(3) Å, b = 18.159(1), c = 10.069(3), b = 97.15(1)°, V = 1025.5(5) $Å^3$, Z = 4, ρ = 1.33 g/cm^3, μ = 8.14 cm^{-1}. Data were collected 4° < 2θ < 120°, with θ/ω scan, ω = (1.00 + 0.15 tanθ)°, no absorption correction, no decay. 11767 reflections were collected and 1403(|Fo| > 3σ|Fo|) reflections were used. The structure was solved by MULTAN78 and difference Fourier synthesis. All hydrogen atom were found in the difference Fourier map. The refinement was carried out by full-matrix least squares with anisotropic temperature factors for the non H-atoms and isotropic temperature factors for H-atoms. (R = 0.063, Rw = 0.074, w = 1/s2(Fo), S = 1.43). Calculations were carried out on a FACOM M-1800/30 with UNICSIII.

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