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SILVER ION-MEDIATED DESULFURIZATION-CONDENSATION OF THIOCARBONYL COMPOUNDS

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Abstract - The title reaction of *N*-hydroxybenzamide with aryl isothiocyanates at ambient temperature gave 5-(arylimino)-3-phenyl-1,4,2-dioxazoles (**1**, **2**) with elimination of Ag_2S. The structure of **1** was determined by X-Ray crystal structure analysis. *N*-Hydroxybenzamide also reacted with diaryl thioketones to afford condensation products, 5,5-diaryl-3-phenyl-1,4,2-dioxazoles(**3**, **4**). Desulfurizations of diaryl thioketones with α-hydroxy acids and with salicylic acid gave in the same way 2,2-diaryl-5-phenyl-1,3-dioxolan-4-ones (**5-8**) and 2,2-diaryl-1,3-benzodioxan-4-ones (**9-11**), respectively. *N*-Phenylglycine and *N*-methylanthranilic acid gave similar types of condensation products (**12**, **13**).

We previously reported that C=C, C=N or acetal bond formation can be readily achieved under mild conditions through silver ion-mediated desulfurization-condensation of some thiocarbonyl compounds with reagents, such as active methylenes and amines, [1~3] Such bond formation occurs only to a small extent when mixtures of these reagents and aldehydes or ketones are subjected to heating in the presence of a strong acid or base. To extend our previous studies, we investigated the desulfurization of aryl isothiocyanates and diaryl thioketones with less reactive reagents such as *N*-hydroxybenzamide and hydroxy acids, which give no condensation products by dehydration with aldehydes or ketones.

We first examined the desulfurization of *N*-hydroxybenzamide with phenyl isothiocyanate or 4-(dimethylamino)phenyl isothiocyanate at ambient temperature by using silver nitrate in the presence of

excess triethylamine. We obtained the condensation products (**1**) and (**2**) in good yield. The structure of **1** was unequivocally established by a single-crystal X-Ray diffraction structure analysis.[4] An ORTEP drawing of the molecular structure of (**1**) is shown in Figure 1. Compound **1** was identified as 5-phenylimino-3-phenyl-1,4,2-dioxazole.

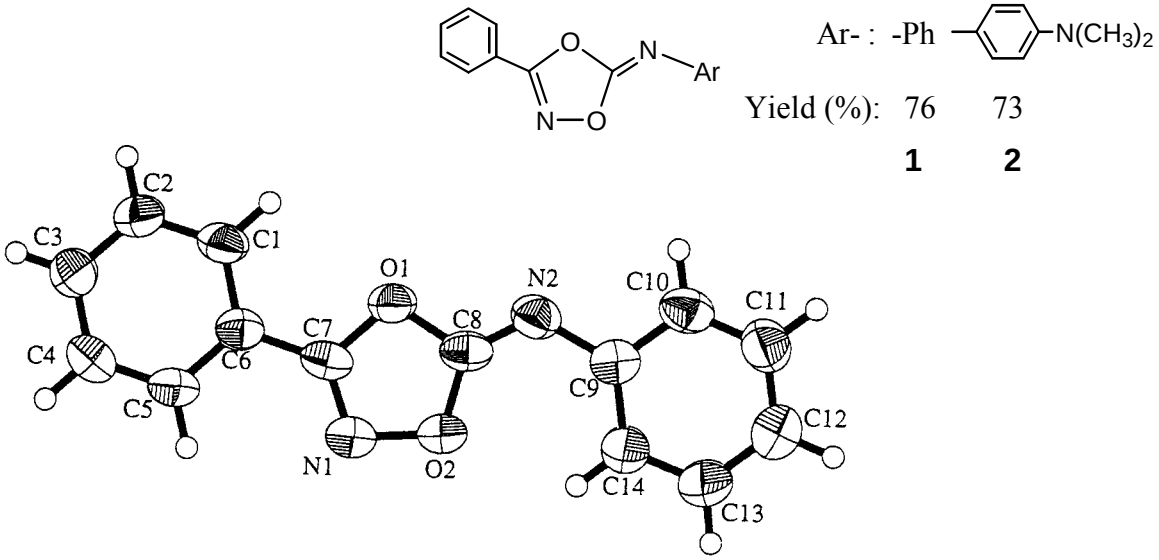
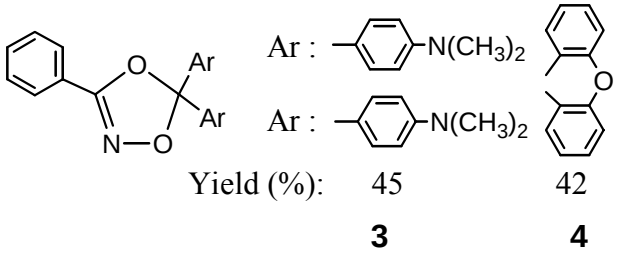


Figure 1. The ORTEP drawing of the molecular structure of **1**

Selected bond length (Å): O1-C7 1.369(4), N1-C7 1.2738(4), O2-N1 1.443(4), O2-C8 1.355(4), O1-C8 1.386(5), N2-C8 1.224(5), N2-C9 1.433(5), C6-C7 1.454(6).

Selected bond angles (°): C7-O1-C8 106.1(3), O1-C7-N1 113.6(4), C7-N1-O2 105.0(3), O1-C8-O2 106.8(4), C8-N2-C9 124.2(4), O1-C7-C6 119.6(3), N1-C7-C6 126.7(4), N2-C9-C10, 115.0(4), N2-C9-C14 126.3(4).

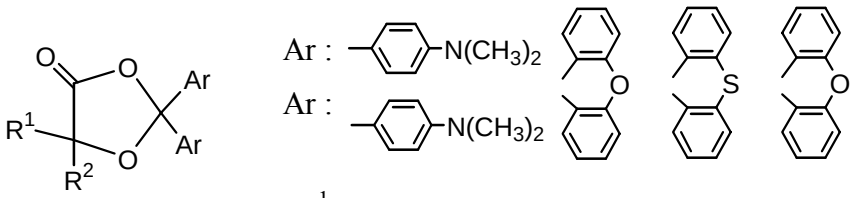
The desulfurizations of 4,4'-bis(dimethylamino)thiobenzophenone and xanthene-9-thione gave the condensation products 5,5-bis[4'-(dimethylamino)phenyl]-3-phenyl-1,4,2-dioxazole (**3**) and spiro[3-phenyl-1,4,2-dioxazole-5,9'-xanthene] (**4**) in moderate yields. This fact showed that *N*-hydroxybenzamide behaves toward thiocarbonyl compounds as the same mode as ethylene glycol or catechol.[2]



In a previous paper[5] we reported that desulfurization of isothiocyanates with α-hydroxy acids affords 1,3-oxazolane-2,4-diones. In the present study, we examined the desulfurization of the thioketones with α-

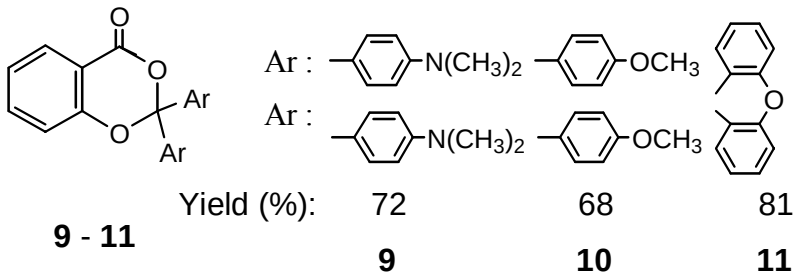
hydroxy acids. We found that 4,4'-bis(dimethylamino)thiobenzophenone reacted with mandelic acid to give 2,2-bis[4'-(dimethylamino)phenyl]-5-phenyl-1,3-dioxolan-4-one (**5**) in good yield. Several other thioketone/α-hydroxy acid pairs also readily gave 1,3-dioxolan-4-ones (**6-8**).

The reaction that affords **5-8** proceeds through direct desulfurization between the hydroxy acids and the thioketones, similar to acetal formation from diols.[2]



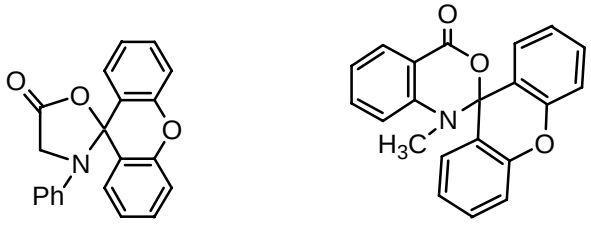
5 - 8

The reaction was applied to 3-hydroxybutyric acid, a β-hydroxy acid, but the expected product, 2,2-diaryl-6-methyl-1,3-dioxan-4-one, was not obtained. On the other hand, reaction with salicylic acid afforded 1,3-benzodioxan-4-ones (**9**, **10**, and **11)** in good yields.



9 - 11

We further examined the desulfurization of thioketones with *N*-substituted amino acids. The reaction of *N*-phenylglycine with xanthene-9-thione gave spiro[3-phenyl-1,3-oxazolidin-5-one-2,9'-xanthene] (**12**), and the reaction of *N*-methylanthranilic acid with xanthene-9-thione gave spiro[3-methyl-1,3-benzoxazin-6-one-2,9'-xanthene] (**13**). We assume that the reaction proceed in the same way as the reactions with the α-hydroxy acids.



12 (80%) **13** (82%)

In conclusion, we found that the silver ion-mediated desulfurization-condensation of thiocarbonyl compounds with moderately active reagents such as *N*-hydroxybenzamide and α-hydroxy acids

proceeded smoothly at ambient temperature. The condensation products, which cannot be obtained by dehydration of the corresponding carbonyl compounds with *N*-hydroxybezamide and α-hydroxy acids, were obtained in good yield.

EXPERIMENTAL

All of the melting points were determined with a Mettler FP82 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300BB spectrometer using tetramethylsilane (TMS) as an internal standard. IR spectra were measured on a JASCO FT-IR5300 spectrophotometer using KBr disks.

5-Phenylimino-3-phenyl-1,4,2-dioxazole (1).

Silver nitrate (410 mg, 2.4 mmol) was added with stirring to a solution of *N*-hydroxybenzaminde (165 mg, 1.2 mmol), phenyl isothiocyanate (135 mg, 1 mmol) and triethylamine (360 mg, 3.6 mmol) in acetonitrile (5 mL), and the mixture was allowed to stand for 5 h at rt. After removal silver sulfide by filtration, the reaction mixture was passed through a silica gel column (Wako gel C-60, hexane: AcOEt = 1:1). The eluent was evaporated *in vacuo*, and the resulting solid was recrystallized from isopropyl ether to give **1**.

Yield 181 mg (76%); mp 90°C. ^{1}H NMR δ 7.13 - 7.90 (*m*); ^{13}C NMR δ 120.42, 123.45, 125.02, 127.09, 129.32, 129.51, 133.66, 142.53, 162.52; IR ν 3061, 1726, 1591, 1364, 1087, 970, 918, 842, 684 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.58; H, 4.25; N, 11.74.

5-[[4'-(Dimethylamino)phenyl]imino]-3-phenyl-1,4,2-dioxazole (2).

N-Hydroxybenzaminde (165 mg, 1.2 mmol), and 4-(dimethylamino)phenyl isothiocyanate (180 mg, 1 mmol) were treated as described above to give **2**.

Yield 202 mg (73%); mp 125 °C. ^{1}H NMR δ 2.95 (*s*, 6H, NMe_2), 6.73 - 7.92 (*m*, 9H); ^{13}C NMR δ 40.95, 112.71, 120.79, 124.67, 126.05, 127.07, 129.23, 129.47, 131.87, 133.49, 148.47, 162.33; IR ν 2897, 1736, 1614, 1520, 1448, 1358, 910, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.29; H, 5.34; N, 14.99.

5,5-Bis[4'-(dimethylamino)phenyl]-3-phenyl-1,4,2-dioxazole (3).

Silver nitrate (410 mg, 2.4 mmol) was added with stirring to a solution of *N*-hydroxybenzamide (165 mg, 1.2 mmol), 4,4'-bis(dimethylamino)thiobenzophenone (284 mg, 1 mmol) and triethylamine (360 mg, 3.6 mmol) in acetontrile (5 mL), and the reaction mixture was allowed to stand for 5 h at rt. After removal of silver sulfide by filtration, the reaction mixture was passed through a silica gel column (Wako gel C-60, hexane: AcOEt = 1:1). The eluent was evaporated *in vacuo*, and the resulting solid was recrystallized from isopropyl

ether to give **3**.

Yield 174 mg (45%); mp 111°C; ^{1}H NMR δ 2.95 (*s*, 8H), 3.05 (*s*, 4H), 6.67 - 6.70 (*m*, 4H), 7.10 – 7.85 (*m*, 9H); ^{13}C NMR δ 40.18, 40.44, 102.46 (quat C), 110.75, 111.67, 117.05, 124.06, 124.94, 126.53, 126.61, 127.08, 128.75, 129.77, 131.39, 132.44, 151.29, 152.97, 158.73; IR ν 2889, 1610, 1525, 1360, 1188, 822 cm^{-1}. Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.30; H, 6.55; N, 10.80.

By the procedure described above, a reagent and a thiocarbonyl compound were treated, respectively, to give **4**–**13**. The reagent; the carbonyl compound; the yield; the melting point; the ^{1}H NMR, ^{13}C NMR, and IR spectral data; and the analytical results are given below.

Spiro[3-phenyl-1,4,2-dioxazole-5,9'-xanthene] (4).

N-Hydroxybenamide; xanthene-9-thione; yield 132 mg (42%); mp 115 °C (isopropyl ether). ^{1}H NMR δ 7.21–7.88 (*m*, 12H), 8.34 – 8.37 (*m*, 1H); ^{13}C NMR ν 107.89 (spiro C), 116.95, 118.20, 118.92, 122.07, 123.18, 124.14, 124.24, 126.98, 127.15, 127.56, 127.99, 131.85, 135.07, 151.30, 156.46, 157.79, 177.57. IR ν 3057, 1608, 1462, 1331, 1215, 1020, 748 cm^{-1}. Anal. Calcd for $C_{20}H_{13}NO_3$: C, 76.18; H, 4.16; N, 4.44. Found: C, 76.13; H, 4.03; N, 4.32.

2,2-Bis[4'-(dimethylamino)phenyl]-5-phenyl-1,3-dioxolan-4-one (5).

Mandelic acid (±form); 4,4'-bis(dimetrhylamino)thiobenzophenone; yellow prisms; yield 323 mg (80.5%); mp 108 °C; ^{1}H NMR δ 2.97 (*s*, 6H, NMe_2), 3.05 (*s*, 6H, NMe_2), 5.21 (*s*, 1H), 6.66 – 7.76 (*m*, 13H); ^{13}C NMR δ 40.03, 72.65, 110.61 (quat C), 111.71, 111.88, 112.08, 126.00, 126.72, 127.19, 127.41, 127.65, 128.18, 128.48, 128.61, 128.76, 129.06, 132.51, 134.11, 138.36, 152.92 (C=O). IR ν 1784 (C=O), 1603, 1234, 1176 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.47; H, 6.50; N, 6.94. Found: C, 74.60; H, 6.51; N, 6.96.

Spiro[2,2-dimethyl-1,3-dioxolan-4-one-2,9'-xanthene] (6).

2-Hdroxy-2-methylpropionic acid; xanthene-9-thione; colorless granules; yield 247 mg (87%); mp 114°C (isopropyl ether). ^{1}H NMR δ 1.66 (*s*, 6H, $2CH_3$), 7.27 – 7.65 (*m*, 8H); ^{13}C NMR δ 26.81 ($2CH_3$), 78.08, 100.55 (spiro C), 117.49, 118.04, 120.73, 123.81, 123.98, 125.20, 125.81, 130.97, 134.91, 151.79, 176.07 (C=O). IR ν 2997, 1803 (C=O), 1456, 1325, 1182 cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.25; H, 4.82. Found: C, 72.33; H, 5.00.

Spiro[5,5-dimethyl-1,3-dioxolan-4-one-2,9'-thioxanthene] (7).

2-Hdroxy-2-methylpropionic acid; thioxanthene-9-thione; yellowish plates; yield 250 mg (84%); mp 122 °C (methanol). ^{1}H NMR δ 1.56 (*s*, 6H, $2CH_3$), 7.26 – 7.84 (*m*, 8H), ^{13}C NMR δ 25.73, 78.10, 103.78 (spiro C), 124.15, 126.59, 127.27, 128.84, 133.28, 133.55, 175.40 (C=O). IR ν 2986, 1811 (C=O), 1288, 1182 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}SO_3$: C, 68.61; H, 4.67; S, 10.96. Found: C, 68.44; H, 4.73; S, 10.75.

Spiro[(±)-2-hexyl-1,3-dioxolan-4-one-2,9'-xanthene] (8).

(±)-2-Hydroxyoctanoic acid; xanthen-9-thione; colorless granules; yield 152 mg (45%); mp 88°C (isopropyl ether). ^{1}H NMR δ 0.88 (*t*, *J* = 7.2 Hz, 3H), 1.31 – 1.56 (*m*, 8H), 1.88 – 2.14 (*m*, 2H), 4.82 (*s*, 0.5H), 4.85 (*s*, 0.5H), 7.26 – 7.66 (*m*, 8H); ^{13}C NMR δ 13.90, 22.39, 25.23, 28.69, 31.41, 32.44, 75.40, 101.74 (spiro C), 117.05, 117.57, 119.18, 120.01, 123.79, 123.83, 125.11, 126.61, 131.15, 131.42, 151.12, 151.77, 173.02 (C=O). IR ν 2953, 2926, 1784 (C=O), 1454, 1329, 1234, 1204 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.56. Found: C, 74.72; H, 6.59.

2,2-Bis[4'-(dimethylamino)phenyl]-1,3-benzodioxan-4-one (9).

Salicylic acid; 4,4'-bis(dimethylamino)thiobenzophenone; yellowish prisms; yield 280 mg (72%); mp 194°C (methanol). ^{1}H NMR δ 2.92 (*s*, 12H), 6.61 – 7.83 (*m*, 12H); ^{13}C NMR δ 40.10, 108.58 (quat C), 111.57, 117.41, 122.41, 127.30, 128.10, 129.70, 136.16, 150.74, 157.17, 162.35 (C=O); IR ν 1736, 1610, 1280, 1238, 1188 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.22; H, 6.23; N, 7.19. Found: C, 74.21; H, 6.23; N, 7.21.

2,2-Bis(4'-methoxyphenyl)-1,3-benzodioxan-4-one (10).

Salicylic acid; 4,4'-dimethoxythiobenzophenone; colorless prisms; yield 246 mg (68%); mp 112°C (methanol). ^{1}H NMR δ 3.77 (*s*, 6H), 6.87 – 7.87 (*m*, 12H); ^{13}C NMR δ 55.21 (CH_3O), 1107.40 (quat C) 113.78, 115.08, 117.44, 122.88, 128.32, 129.83, 131.94, 136.50, 156.72, 160.21, 161.63. IR ν 1743, 1610, 1305, 1253, 1176 cm^{-1}. Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.86; H, 5.00. Found: C, 72.92; H, 5.01.

Spiro[1,3-benzodioxan-4-one-2,9'-xanthene] (11).

Salicylic acid; xanthene-9-thione; colorless prisms; yield 256 mg (81%); mp 182°C (ethyl acetate/ hexane). ^{1}H NMR δ 6.86 – 8.12 (*m*); ^{13}C NMR δ 98.85 (spiro C), 113.32, 117.21, 117.31, 120.18, 123.16, 123.60, 125.86, 129.60, 131.31, 137.14, 150.94, 155.75, 160.28. IR ν 1741, 1460, 1300, 1236, 754 cm^{-1}. Anal. Calcd for $C_{20}H_{12}O_4$: C, 76.02; H, 3.74. Found: C, 75.94; H, 3.82.

Spiro[3-phenyl-1,3-oxazolidin-5-one-2,9'-xanthene] (12).

N-Phenylglycine; xanthene-9-thione; colorless needles; yield 263 mg (80%); mp 154 °C (methanol); ^{1}H NMR δ 4.68 (*s*, 2H), 6.34 – 7.77 (*m*, 13H); ^{13}C NMR δ 49.96, 92.49 (spiro C), 113.81, 117.47, 118.03, 119.02, 124.00, 124.22, 126.81, 129.13, 129.50, 131.43, 134.94, 141.04, 152.19, 168.29. IR ν 1793, 1454, 1242, 748 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.45; H, 4.48; N, 4.08.

Spiro[3-methyl-1,3-benzoxazin-6-one-2,9'-xanthene] (13).

N-Methylanthranilic acid; xanthene-9-thione; colorless granules; yield 270 mg (82%); mp 174 °C

(ethyl acetate/hexane); ^{1}H NMR δ 2.59 (s, 3H), 6.79 – 8.05 (*m*, 12H); ^{13}C NMR δ 33.80, 89.91 (spiro C), 110.51, 111.33, 117.28, 118.35, 120.21, 123.88, 126.78, 130.84, 131.09, 136.78, 148.67, 150.92, 160.64. IR ν 1718, 1552, 1105, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 76.48; H, 4.42; N, 4.13.

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

   A crystal of having approximate dimension of 0.2 x 0.4 x 0.2 mm was used. X-Ray data were collected on a Rigaku AFC7R diffractometer by using graphite-monochromatized MoKα radiation (λ = 0.71069 Å). Crystal data : $C_{14}H_{10}N_2O_2$, monoclinic, space group $P2_{1/n}$, a = 14.019(4) Å, b = 5.328(5), c = 15.708(5), β = 94.97(2)°, V = 1168(1) Å^3, Z = 4, D_{calc} = 1.354 g/cm^3, m = 0.93 cm^{-1}. The data were collected at - 30 °C using the ω - 2θ scan technique to a maximum 2θ value of 55.0 °. An empirical absorption correction (transmission factors: 0.9497 - 0.9816). 2761 Reflections were collected and 1073(I > 3.00 σ(I)) reflections were used. The structure was solved by SHELX97 (Sheldrick, G. M. (1997), Program for solution of Crystal Structures University of Goettingen, Germany) and difference Fourier synthesis. All hydrogen atoms were found in the difference Fourier map. The refinement was carried out by full-matrix least squares with anisotropic temperature factors for the non-hydrogen atoms and hydrogen atoms were all fixed at the last stage. (R = 0.052, Rw = 0.062, w = 1/s2(Fo), S = 2.08). Calculations were carried out with Texsan (Crystal Structure Analysis Package, Molecular Structure Corporation (1992)).
5. I. Shibuya, M. Goto, M. Shimizu, M. Yanagisawa, and Y. Gama, *Heterocycles*, 1999, **51**, 2667.