SILVER ION–MEDIATED DESULFURIZATION OF N,N-DISUBSTITUTED 2-HYDROXYTHIOBENZAMIDES

Isao Shibuya,* Kazumasa Honda, Yasuo Gama, and Masao Shimizu

National Institute of Advanced Industrial Science and Technology (AIST)
1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

Abstract - Silver ion–mediated desulfurization of N-(2-hydroxythiobenzoyl)morpholine (1a) or -piperidine (1b) was used to develop a new synthetic method for heterocycles such as 1,3-benoxazin-1-ium salts. 2-Amino-4-morpholino- and 2-amino-4-piperidino-1,3-benoxazin-1-ium perchlorate (2a, 2b) or 2-(N,N-dimethylamino)-4-morpholino- and 2-(N,N-dimethylamino)-4-piperidino-1,3-benoxazin-1-ium perchlorate (3a, 3b) were obtained by treatment of 1a and 1b, respectively, with silver perchlorate in the presence of excess cyanamide or N,N-dimethylcyanamide, and the structure of 3a was confirmed by X-Ray crystallography. Desulfurization of 1 with AgOCN afforded 1,3-benoxazin-2-ones (4). In addition, treatment of 1 with methyl cyanoacetate in the presence of silver trifluoroacetate and triethylamine gave 3-cyanochromen-2-ones (5).

In earlier papers¹,² we reported that desulfurization of thiocarbonyl compounds with amines, active methylenes, or alcohols readily gave imines, olefins, or acetals, respectively, in the presence of a silver salt under mild basic conditions. This reaction is considered to proceed by a condensation reaction between the thiocarbonyl compounds and the reagents. In addition, we reported new reactions giving 5-azauracil and quinazoline derivatives through the cyclodesulfurization of N-thiocarbonylarylamines in the presence of silver salts.³⁴ Such heterocycle-forming reactions have
never been reported for N-carbonylarylamines. This fact suggests that the desulfurization in the presence of silver salts is further applicable to organic synthesis, and in order to develop a new technique for synthesizing heterocycles, we investigated the desulfurization reactions of \( N,N \)-disubstituted 2-hydroxythiobenzamides with various reagents. As a result, we discovered some unique heterocycle-forming reactions.

We prepared the starting materials, \( N \)-(2-hydroxythiobenzoyl)morpholine (1a) and -piperidine (1b) by heating a mixture of salicylaldehyde and sulfur in an excess of the appropriate secondary amine.\(^5\) We then treated 1a and 1b with 2.4 mol equiv of silver perchlorate and excess cyanamide in refluxing propionitrile for 1 h and obtained 2a and 2b in 74% yield and 61% yield, respectively, with liberation of silver sulfide. Similarly, 3a and 3b were obtained in 69% yield and 61% yield, respectively, when 1a and 1b were treated with \( N,N \)-dimethylcyanamide at 130 °C for 1 h. Moreover, treatment of 1b with silver trifluoromethanesulfonate also gave 3c in 57% yield.

In the \(^{13}\)C NMR spectra of 2a and 2b, the eight signals assigned to the carbons of the 1,3-benoxazin-1-ium ring were observed in the 110–161 ppm range. The IR spectra of these compounds had a broad N–H stretching absorption in the 3400–3150 cm\(^{-1}\) range, three absorptions corresponding to the heterocycle in the 1670–1550 cm\(^{-1}\) range, and a strong absorption (ClO\(_4\)) at around 1090 cm\(^{-1}\). The spectroscopic and analytical data suggest that 2a and 2b are 2--amino-4-morpholino- and 2-amino-4-piperidino-1,3-benoxazin-1-ium perchlorate, respectively.

\[
\begin{array}{c|cccc}
 & 2a & 2b & 3a & 3b \\
\hline
-NR_2 & - & \text{-} & \text{-} & \text{-} \\
-NR'_2 & \text{-NH}_2 & \text{-NH}_2 & \text{-N(CH}_3)_2 & \text{-N(CH}_3)_2 \\
\end{array}
\]

The spectroscopic data indicate that the skeleton of 3 is identical to that of 2: the \(^1\)H and \(^{13}\)C NMR data and the IR spectra of 3 are similar to those of 2 except for the differences due to the amino and dimethylamino groups. The molecular structure of 3a was unequivocally established by a single-crystal X-Ray diffraction analysis. The ORTEP drawing shown in Figure 1 identifies 3a as 2-(\(N,N\)-dimethylamino)-4-morpholino-1,3-benoxazin-1-ium perchlorate.\(^6\)
Selected bond lengths (Å): O(1)–C(1) 1.355(3), N(1)–C(1) 1.305(3), N(1)–C(2) 1.345(3), C(2)–C(3) 1.459(3), C(3)–C(8) 1.392(4), O(1)–C(8) 1.379(3), C(3)–C(4) 1.398(4), C(4)–C(5) 1.380(4), C(5)–C(6) 1.399(4), C(6)–C(7) 1.364(5), C(7)–C(8) 1.377(4), N(2)–C(2) 1.325(3), N(3)–C(1) 1.311(3).

Figure 1. ORTEP drawing of 3a

Selected bond angles (°): C(1)–O(1)–C(8) 116.8(2), O(1)–C(1)–N(1) 125.0(3), C(1)–N(1)–C(2) 118.3(2), N(1)–C(2)–C(3) 119.3(2), C(2)–C(3)–C(8) 115.6(2), O(1)–C(8)–C(3) 120.9(3), C(4)–C(5)–C(6) 119.6(3), C(5)–C(6)–C(7) 120.8(3), C(6)–C(7)–C(8) 118.4(3), C(3)–C(8)–C(7) 123.3(3), O(1)–C(8)–C(7) 116.4(3), O(1)–C(1)–N(3) 113.1(3), N(1)–C(1)–N(3) 121.8(3), N(1)–C(2)–N(2) 116.8(2), N(2)–C(2)–C(3) 123.9(3).

The proposed reaction pathway leading to these products is shown in Scheme 1. The electron-donating amino group attached directly to the cyano group of cyanamide greatly enhances its nucleophilicity. The initial attack of the cyano group on the thiocarbonyl carbon of 1 is mediated by the added silver ion. The addition of another silver ion to the thiocarbonyl sulfur atom and the subsequent liberation of silver sulfide give the desired products.

Scheme 1

Next we examined the desulfurization of 1 with silver cyanate. On refluxing in acetonitrile with 2.4 mol equiv of silver cyanate for 1 h, 1a and 1b gave 4a and 4b, respectively, in a good yield together
with silver sulfide, and the spectroscopic and analytical data show that 4a and 4b are 4-morpholino-
and 4-piperidino-1,3-benzoxazin-2-one, respectively. A plausible pathway for the formation of 4 is
shown in Scheme 2.

During the desulfurization, the cyanate anion behaves as a nucleophile, attacks the thiocarbonyl
carbon activated by the addition of silver ion, and is incorporated into the product as a building block
of the heterocycle.

In addition, we also examined the desulfurization of 1 with a silver salt and an active methylene
under basic conditions. On refluxing in acetonitrile with silver trifluoroacetate and methyl
cyanoacetate for 1 h in the presence of excess triethylamine, 1a and 1b gave 5a and 5b in 47%
yield and 41% yield, respectively, with liberation of silver sulfide. Silver trifluoromethanesulfonate
could also be used for this reaction, and it gave 5b in 37% yield.

Again, the spectroscopic data indicate that the structure of 5 is analogous to that of 4: the data for 5
are similar to those for 4, except for the data ascribed to the cyano group. The analytical results
show that these compounds are 3-cyano-4-morpholino- and 3-cyano-4-piperidinochromen-2-one
(5a, 5b). The pathway for the formation of these products is shown in Scheme 3. The carbanion
generated from methyl cyanoacetate initially attacks the thiocarbonyl carbon of 1, which is activated
by the addition of silver ion; and the subsequent attack of another silver ion induces cyclization to
form 5 with the elimination of silver sulfide and methanol.

In conclusion, we have developed a new synthetic method for 1,3-benzoxazin-1-ium salts, 1,3-
benzoxazin-2-ones, and 3-cyanochromen-2-ones through silver ion–mediated desulfurization of 

N,N-disubstituted 2-hydroxythiobenzamides.

EXPERIMENTAL

Melting points were determined on a Mettler FP90 microscope plates and is uncorrected. $^1$H and $^{13}$C NMR spectra were obtained with a Varian Gemini 300 BB (300 MHz) spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer on KBr disks. High-resolution mass spectra were determined on a Hitachi M-80B instrument by the direct introduction method.

$N$-(2-Hydroxythiobenzoyl)morpholine ($1a$) and $N$-(2-hydroxythiobenzoyl)piperidine ($1b$)

A mixture of salicylaldehyde (2.44 g, 20 mmol), sulfur (0.96 g, 30 mmol), and morpholine or piperidine (4 mL) was heated to 130 °C for 3 h. The product was recrystallized from the resulting mixture with ethanol to give 3.48 g (78%) of $1a$ (mp 167–168 °C, lit.5 167 °C) or 3.23 g (73%) of $1b$ (mp 146–147 °C, lit.,5 146.5 °C), respectively.

$2$-Amino-$4$-morpholino-$1,3$-benzoxazin-1-iium perchlorate ($2a$)

To a solution of $N$-(2-hydroxythiobenzoyl)morpholine ($1a$) (223 mg, 1 mmol) and cyanamide (210 mg, 5 mmol) in propionitrile (5 mL) was added silver perchlorate (500 mg, 2.4 mmol) with stirring, and the reaction mixture was heated at reflux for 1 h. After removal of silver sulfide by filtration and evaporation of the solvent under reduced pressure, the resulting residue was recrystallized from methanol to give $2a$.

Colorless granules; yield 245 mg (74%); mp 285–287 °C. $^1$H NMR (DMSO-$d_6$) δ 3.81 (br s, 4H), 4.17 (br s, 4H), 7.51–7.59 (m, 2H), 7.88–7.92 (m, 1H), 8.07–8.09 (m, 1H), 9.34 (br s, 2H). $^{13}$C NMR δ 46.69, 51.44, 65.56 (2C), 110.69, 117.06, 125.49, 127.56, 136.12, 153.49, 157.84, 160.82. IR ν 3354, 3295, 3159, 1678, 1599, 1555, 1084 (ClO$_4$–) cm$^{-1}$. Anal. Calcd for C$_{12}$H$_{14}$N$_3$O$_6$Cl: C, 43.45; H, 4.25; N, 12.67. Found: C, 43.41; H, 4.13; N, 12.40.

$2$-Amino-$4$-piperidino-$1,3$-benzoxazin-1-iium perchlorate ($2b$)

Treatment of $N$-(2-hydroxythiobenzoyl)piperidine ($1b$) (221 mg, 1 mmol) according to the procedure used to prepare $2a$ gave $2b$.

Colorless granules; yield 200 mg (61%); mp 205–207 °C. $^1$H NMR (DMSO-$d_6$) δ 1.76 (br s, 6H), 4.09
(br s, 4H), 7.52–7.57 (m, 2H), 7.86–8.03 (m, 2H), 9.23 (s, 2H). $^{13}$C NMR $\delta$ 23.06, 25.20, 26.01, 48.05, 51.83, 110.84, 117.06, 125.52, 127.56, 135.92, 153.42, 157.63, 160.09. IR $\nu$ 3397, 3287, 3229, 1672, 1602, 1550, 1107 (ClO$_4^-$). Anal. Calcd for C$_{13}$H$_{16}$N$_3$O$_5$Cl: C, 47.35; H, 4.89; N, 10.75. Found: C, 47.30; H, 4.79; N, 10.74.

2-(N,N-Dimethylamino)-4-morpholino-1,3-benzoxazin-1-ium perchlorate (3a)

To a solution of 1a (223 mg, 1 mmol) in N,N-dimethylcyanamide (4 mL) was added silver perchlorate (500 mg, 2.4 mmol) with stirring, and the reaction mixture was heated to 130 °C for 1 h. After removal of silver sulfide by filtration and evaporation of the solvent in vacuo, the resulting residue was recrystallized from ethanol to give 3a.

Yellow plates; yield 248 mg (69%); mp 226–228 °C. $^1$H NMR (DMSO-d$_6$) $\delta$ 3.28 (s, 3H), 3.31 (s, 3H), 3.80 (br s, 4H), 4.20 (br s, 4H), 7.52–7.57 (m, 1H), 7.69–7.72 (m, 1H), 7.89–7.95 (m, 1H), 8.07–8.11 (m, 1H). $^{13}$C NMR $\delta$ 36.79, 38.02, 47.01, 51.60, 65.97 (2C), 110.90, 117.82, 126.11, 127.97, 136.52, 154.24, 155.65, 160.18. IR $\nu$ 3065, 2990, 2939, 1657, 1602, 1560, 1410, 1091, 763 cm$^{-1}$. Anal. Calcd for C$_{14}$H$_{18}$N$_3$O$_6$Cl: C, 46.74; H, 5.04; N, 11.68. Found: C, 46.57; H, 5.04; N, 11.52.

2-(N,N-Dimethylamino)-4-piperidino-1,3-benzoxazin-1-ium perchlorate (3b)

Treatment of 1b (221 mg, 1 mmol) according to the procedure used to prepare 3a gave 3b.

Yellow granules; yield 220 mg (61%); mp 206–208 °C (ethanol). $^1$H NMR (DMSO-d$_6$) $\delta$ 1.77 (br s, 6H), 3.26 (s, 3H), 3.29 (s, 3H), 4.10 (br s, 4H), 7.53–7.57 (m, 1H), 7.66–7.69 (m, 1H), 7.88–7.92 (m, 1H), 8.01–8.03 (m, 1H). $^{13}$C NMR $\delta$ 23.39 (3C), 36.75, 37.99, 48.48, 53.49, 110.80, 117.59, 125.89, 127.80, 136.03, 155.11, 159.17. IR $\nu$ 3065, 2990, 2939, 1657, 1602, 1560, 1410, 1091, 763 cm$^{-1}$. Anal. Calcd for C$_{15}$H$_{20}$N$_3$O$_5$Cl: C, 50.35; H, 5.63; N, 11.74. Found: C, 50.26; H, 5.59; N, 11.52.

2-(N,N-Dimethylamino)-4-piperidino-1,3-benzoxazin-1-ium trifluoromethanesulfonate (3c)

According to the procedure described above for the preparation of 3a, 1b (221 mg, 1 mmol) was treated with silver trifluoromethanesulfonate (617 mg, 2.4 mmol) to give 3c.

Colorless granules; yield 232 mg (57%); mp 176–177 °C (methanol). $^1$H NMR (DMSO-d$_6$) $\delta$ 1.78 (br s, 6H), 3.26 (s, 3H), 3.29 (s, 3H), 4.10 (br s, 4H), 7.53–7.57 (m, 1H), 7.66–7.69 (m, 1H), 7.88–7.92 (m, 1H), 8.00–8.03 (m, 1H). $^{13}$C NMR $\delta$ 23.61, 25.69, 26.59, 36.94, 38.20, 48.75, 52.28, 110.97, 117.81, 126.15, 127.85, 136.27, 154.00, 155.32, 159.37. IR $\nu$ 3065, 2941, 1655, 1597, 1555, 1402, 1269, 1143, 1032, 763, 636 cm$^{-1}$. Anal. Calcd for C$_{16}$H$_{20}$N$_3$O$_4$F$_3$S: C, 47.17; H, 4.95; N, 10.31. Found: C, 47.13; 4.64; N, 10.31.
4-Morpholino-1,3-benzoxazin-2-one (4a)

Silver cyanate (360 mg, 2.4 mmol) was added to a solution of 1a (223 mg, 1 mmol) in acetonitrile (5 mL) with stirring, and the reaction mixture was heated at reflux for 1 h. After removal of silver sulfide by filtration, the solution was passed through a silica gel column (Silica Gel 60 Cica-Reagent, ethyl acetate), and the resulting eluent was evaporated *in vacuo*. Recrystallization of the residue from ethanol gave 4a.

Colorless needles; yield 186 mg (80%); mp 179 ° (ethanol). $^1$H NMR (CDCl$_3$) $\delta$ 3.82–3.85 (m, 4H), 4.07–4.10 (m, 4H), 7.22–7.34 (m, 2H), 7.60–7.67 (m, 2H). $^{13}$C NMR $\delta$ 49.03 (2C), 66.92 (2C), 110.26, 118.26, 123.34, 126.01, 135.08, 153.05, 157.97, 165.57. IR $\nu$ 2920, 1707, 1597, 1531, 1315, 1111, 756 cm$^{-1}$. Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.92; H, 5.12; N, 12.07.

4-Piperidino-1,3-benzoxazin-2-one (4b)

According to the procedure described above for the preparation of 4a, 1b (221 mg, 1 mmol) was treated with silver cyanate to give 4b.

Colorless syrup; yield 216 mg (94%). $^1$H NMR (CDCl$_3$) $\delta$ 1.80 (br s, 6H), 3.97 (br s, 4H), 7.22–7.27 (m, 2H), 7.57–7.70 (m, 2H). $^{13}$C NMR $\delta$ 24.30, 26.24 (2C), 49.89 (2C), 110.70, 117.82, 123.24, 126.48, 134.65, 153.38, 157.67, 164.96. IR $\nu$ 2937, 2856, 1716, 1595, 1531, 1312, 1095, 916, 752 cm$^{-1}$. HRMS m/z: Calcd for C$_{13}$H$_{14}$N$_2$O$_2$, 230.1055; found, 230.1026 (M$^+$).

3-Cyano-4-morpholinochromen-2-one (5a)

To a solution of 1a (223 mg, 1 mmol), triethylamine (360 mg, 3.6 mmol), and methyl cyanoacetate (120 mg, 1.2 mmol) in acetonitrile (5 mL) was added silver trifluoroacetate (530 mg, 2.4 mmol) with stirring, and the reaction mixture was heated at reflux for 1 h. After removal of silver sulfide by filtration and evaporation of the solvent *in vacuo*, the resulting residue was recrystallized from acetonitrile to give 5a.

Pale yellow granules; yield 120 mg (47%); mp 235 °. $^1$H NMR (DMSO-$d_6$) $\delta$ 3.35 (s, 4H), 3.85 (s, 4H), 7.37–7.45 (m, 2H), 7.70–7.76 (m, 1H), 7.85–7.87 (m, 1H). $^{13}$C NMR $\delta$ 49.57 (2C), 63.26 (2C), 78.10, 111.87, 113.57, 114.59, 121.22, 124.11, 131.31, 150.04, 156.72, 160.54. IR $\nu$ 3050, 2955, 2210, 1699, 1531, 1311, 1111, 912, 754 cm$^{-1}$. Anal. Calcd for C$_{14}$H$_{12}$N$_2$O$_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.49; H, 4.60; N, 10.86.

3-Cyano-4-piperidinochromen-2-one (5b)
According to the procedure described above for the preparation of 5a, 1b (221 mg, 1 mmol) was treated with methyl cyanoacetate to afford 5b.

Pale yellow granules; yield 105 mg (41%); mp 209 ° (ethyl acetate). 1H NMR (CDCl3) δ 1.86–1.92 (br s, 6H), 3.78–3.82 (br s, 4H), 7.28–7.35 (m, 2H), 7.58–7.71 (m, 2H). 13C NMR δ 23.84, 26.67 (2C), 54.36 (2C), 83.34, 115.96, 116.50, 118.63, 124.35, 126.53, 134.28, 154.12, 160.63, 164.97. IR ν 2943, 2858, 2212, 1697, 1593, 1531, 1300, 758 cm⁻¹. Anal. Calcd for C15H14N2O2: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.63; H, 5.52; N, 11.03.

Treatment of 1b (221 mg, 1 mmol) with silver trifluoromethanesulfonate (617 mg, 2.4 mmol) and methyl cyanoacetate according to the procedure described above for the preparation of 5a gave 94 mg of 5b (37%).

REFERENCES AND NOTES
6. A yellow transparent needle crystal of 3a with dimensions of 0.83 x 0.19 x 0.08 mm was used for the X-ray analysis. Data collection was carried out using a Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation. Crystal data: C14H18N3O6Cl, FW = 359.77, monoclinic space group P2₁/n, a = 14.601(1) Å, b = 7.9464(6) Å, c = 13.864(1) Å, β = 95.929(8)°, V = 1600.1(2) Å³, Z = 4, Dc = 1.49 g cm⁻³, μ = 0.276 mm⁻¹. Intensity data: 3° ≤ 2θ ≤ 55° with ω-scans. Intensity data were corrected for Lorentz and polarization factors, and linear decay corrections were applied. Three intensity standard reflections showed 1.7% intensity loss. No absorption correction was applied. Of the 4390 collected reflections, 4261 unique reflections were used for the analysis (Rint = 0.0124). The structure was solved by a direct method (SHELXS86). All the hydrogen atoms were located using difference Fourier
maps. The refinement was carried out by a full-matrix least-squares method on $F^2$ with anisotropic thermal parameters for the non-H atoms and isotropic parameters for the H atoms ($R_1 = 0.054$, $R_2 = 0.0674$, $S = 2.15$). All the calculations were carried out on a Silicon Graphics O2 workstation with teXsan software. An ORTEP drawing of the molecular structure of 3a is shown in Figure 1.8

