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

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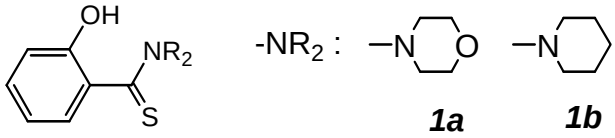
Abstract - Silver ion–mediated desulfurization of *N*-(2-hydroxythiobenzoyl)morpholine (***1a***) or -piperidine (***1b***) was used to develop a new synthetic method for heterocycles such as 1,3-benzoxazin-1-ium salts. 2-Amino-4-morpholino- and 2-amino-4-piperidino-1,3-benzoxazin-1-ium perchlorate (***2a***, ***2b***) or 2-(*N,N*-dimethylamino)-4-morpholino- and 2-(*N,N*-dimethylamino)-4-piperidino-1,3-benzoxazin-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-benzoxazin-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 papers[1,2] 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.[3,4] 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.

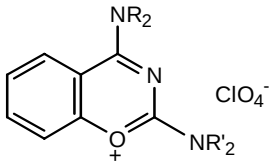
We prepared the starting materials, *N*-(2-hydroxythiobenzoyl)morpholine (***1a***) and -piperidine (***1b***) by heating a mixture of salicylaldehyde and sulfur in an excess of the appropriate secondary amine.[5] We then treated ***1a*** and ***1b*** with 2.4 mol equiv of silver perchlorate and excess cyanamide in



1a ***1b***

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 ^{o}C for 1 h. Moreover, treatment of ***1b*** with silver trifluoromethanesulfonate also gave ***3c*** in 57% yield.

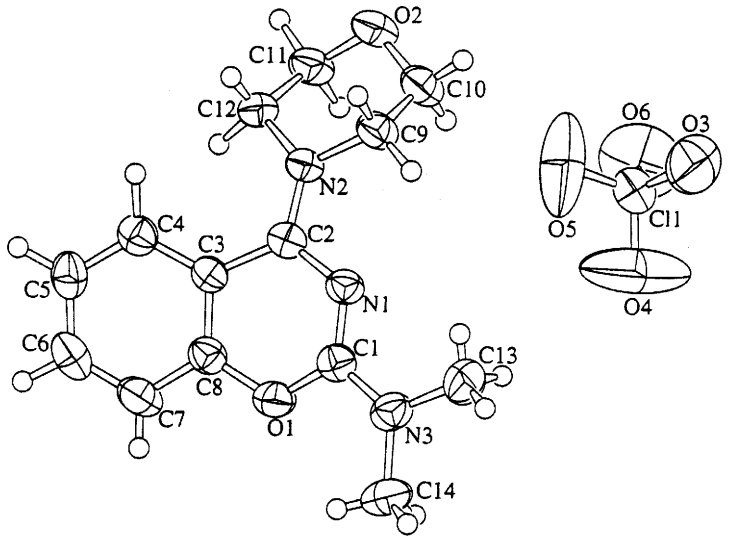
In the ^{13}C NMR spectra of ***2a*** and ***2b***, the eight signals assigned to the carbons of the 1,3-benzoxazin-1-ium ring were observed in the 110–161 ppm range. The IR spectra of these compounds had a broad N–H stretching absorption in the 3400–3150 cm^{-1} range, three absorptions corresponding 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-benzoxazin-1-ium perchlorate, respectively.



2a, 2b, 3a, 3b

	2a	***2b***	***3a***	***3b***
-NR_2				
-NR'_2	-NH_2	-NH_2	-$N(CH_3)_2$	-$N(CH_3)_2$

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-benzoxazin-1-ium perchlorate.[6]

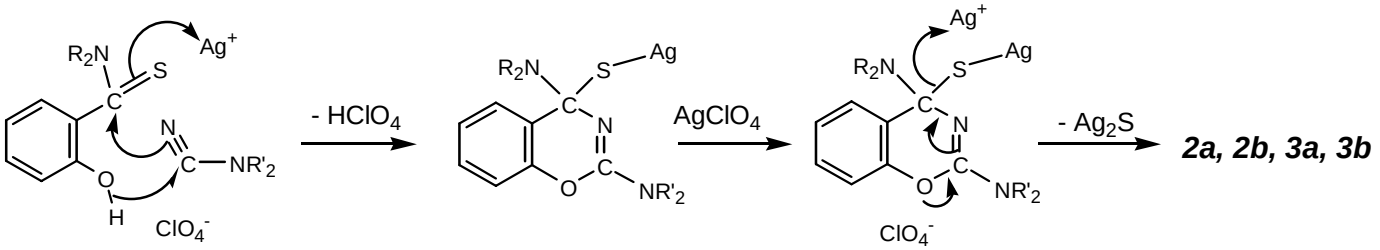


Selected bond lengths (Å): O(1)–C(1) 1.355(3), N(1)–C(1) 1.305(3), N(1)–C(2) 1.345(3), C(2)–C(3) 1.459(3), C(3)–C(8) 1.392(4), O(1)–C(8) 1.379(3), C(3)–C(4) 1.398(4), C(4)–C(5) 1.380(4), C(5)–C(6) 1.399(4), C(6)–C(7) 1.364(5), C(7)–C(8) 1.377(4), N(2)–C(2) 1.325(3), N(3)–C(1) 1.311(3).

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) 120.3(3), C(2)–C(3)–C(4) 127.6(3), C(4)–C(3)–C(8) 116.7(3), C(3)–C(4)–C(5) 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).

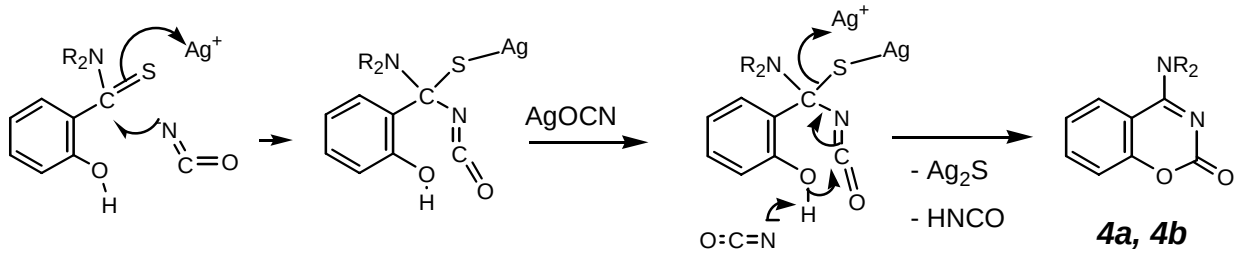
The proposed reaction pathway leading to these products is shown in Scheme 1. The electron-donating amino group attached directly to the cyano group of cyanamide greatly enhances its nucleophilicity. The initial attack of the cyano group on the thiocarbonyl carbon of ***1*** is mediated by the added 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.

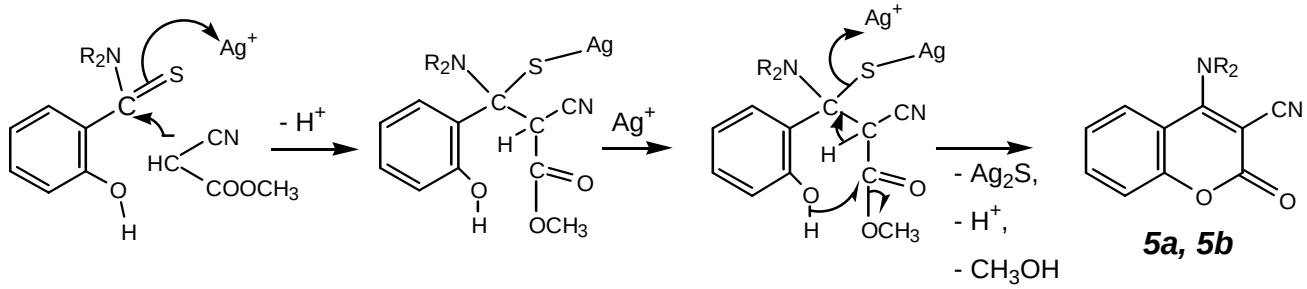


Scheme 2

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.



Scheme 3

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 ^{o}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 ^{o}C, lit.,[5] 167 ^{o}C) or 3.23 g (73%) of ***1b*** (mp 146–147 ^{o}C, lit.,[5] 146.5 ^{o}C), respectively.

2-Amino-4-morpholino-1,3-benzoxazin-1-ium 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 ^{o}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 $C_{12}H_{14}N_3O_6Cl$: 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-ium 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 ^{o}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 δ 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 ν 3397, 3287, 3229, 1672, 1602, 1550, 1107 (ClO_4^-). Anal. Calcd for $C_{13}H_{16}N_3O_5Cl$: 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) δ 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 δ 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 ν 3065, 2990, 2939, 1657, 1602, 1560, 1410, 1091, 763 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_3O_6Cl$: 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) δ 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 δ 23.39 (3C), 36.75, 37.99, 48.48, 53.49, 110.80, 117.59, 125.89, 127.80, 136.03, 153.78, 155.11, 159.17. IR ν 3065, 2990, 2939, 1657, 1602, 1560, 1410, 1091, 763 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_3O_5Cl$: 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) δ 1.78 (*br s*, 6H), 3.26 (*s*, 3H), 3.29 (*s*, 3H), 4.10 (*br s*, 4H), 7.53–7.57 (*m*, 1H), 7.66–7.68 (*m*, 1H), 7.88–7.92 (*m*, 1H), 8.00–8.03 (*m*, 1H). ^{13}C NMR δ 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 ν 3065, 2941, 1655, 1597, 1555, 1402, 1269, 1143, 1032, 763, 636 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_3O_4F_3S$: 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 ($CDCl_3$) δ 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 δ 49.03 (2C), 66.92 (2C), 110.26, 118.26, 123.34, 126.01, 135.08, 153.05, 157.97, 165.57. IR ν 2920, 1707, 1597, 1531, 1315, 1111, 756 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$: 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 ($CDCl_3$) δ 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 δ 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 ν 2937, 2856, 1716, 1595, 1531, 1312, 1095, 916, 752 cm^{-1}. HRMS *m/z:* Calcd for $C_{13}H_{14}N_2O_2$, 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) δ 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 δ 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 ν 3050, 2955, 2210, 1699, 1531, 1311, 1111, 912, 754 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2O_3$: 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). ^{1}H NMR ($CDCl_3$) 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). ^{13}C 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 $C_{15}H_{14}N_2O_2$: 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%).

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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: $C_{14}H_{18}N_3O_6Cl$, FW = 359.77, monoclinic space group $P2_1/n$, a = 14.601(1) Å, b = 7.9464(6) Å, c = 13.864(1) Å, β = 95.929(8)°, V = 1600.1(2) Å^3, Z = 4, D_c = 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 (R_{int} = 0.0124). The structure was solved by a direct method (*SHELXS*86).[7] 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.[8] An ORTEP drawing of the molecular structure of ***3a*** is shown in Figure 1.[9]

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