Synthesis of 3-Substituted Benzoazoline-2-thiones

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Several methods for the preparations of 3-substituted benzoazoline-2-thiones (1) were examined. Method B via the thiation of 3-substituted benzoazolin-2-one (5) with phosphorus pentasulfide was found to be applicable to the preparation of most analogs of 1, with a few exceptions. Method C via the cyclization of 2-(alkylamino)phenol (7) with potassium O-methylthiocarbonate was suitable for the preparation of analogs with a group sensitive to high temperature or with an aryl- (including aromatic heterocyclic ring) methyl group.

In addition, the reaction of benzoazoline-2-thione (2) with acetals such as 1-ethoxyisochroman, 2-ethoxytetrahydrofuran, and 2-ethoxytetrahydropyran, or with Michael acceptors such as 2,3-dihydrofuran and 2H-3,4-dihydropyran, gave 3-substituted benzoazoline-2-thione (1d–f).

Keywords—3-substituted benzoazoline-2-thione; 3-substituted benzoazolin-2-one; 2-(alkylthio)benzoxazole; 2-(alkylamino)phenol; acetal; Michael acceptor; thiation; UV spectra

Benzoazoline-2-thiones have been reported to exhibit diverse biological properties. In particular, 3-methyl and 3-ethylbenzoazoline-2-thiones were reported to have fungicidal activity.1 Furthermore, 3-(N-substituted aminomethyl)benzoazoline-2-thiones display bacteriocidal2b,3a and spasmylytic3 activities. However, there have been few reports on the preparation of benzoazoline-2-thiones3,8 with a substituent other than acyl, N,N-dialkylaminoethyl, methyl, or ethyl at position 3. These facts prompted us to search for a general method for the preparation of 1 with a variety of substituents at position 3.

Three possible methods (A, B, and C) for the preparation of 1 (shown in Chart 1) were examined. At first, 3-benzylbenzoazoline-2-thione (1c) was prepared by these methods in order to compare them. The overall yields of 1c from 2-aminophenol were 60 (method A), 50 (method B), and 81% (method C).

Method A involves an alkylation process of benzoazoline-2-thiones (2). The alkylation of 2 with several alkylating agents, such as diazomethane,4 dimethyl sulfate,4,5 or alkyl halides with a phase transfer catalyst,6 has been found to give 2-(alkylthio)benzoxazole (3) as the main product.

However, in our present investigation, some analogs of 1 were found to be obtained from 2. The reaction of 2 with tert-butyl bromide gave 3-tert-butylbenzoazoline-2-thione (1b) in higher yield (19%) than that (5%) of 2-(tert-butylthio)benzoxazole7 (3b). On the basis of the previous finding that 1-ethoxyisochroman readily reacted with the nitrogen atom of acetalamide to give 1-acetamidoisochroman,8 the reaction of 2 with 1-ethoxyisochroman was examined. 3-(1-ISochromany1)benzoazoline-2-thione (1d) was obtained in 85% yield. This result suggested that acetals, such as 2-ethoxytetrahydrofuran and 2-ethoxytetrahydropyran, may react with 2 to give the corresponding 3-substituted benzoazoline-2-thiones. Actually, 3-(2-tetrahydrofuryl)benzoazoline-2-thione (1e) and 3-(2-tetrahydropyranyl)benzoazoline-2-thione (1f) were obtained in 52 and 75% yields, respectively. Compounds 1e and f were also
prepared by the reaction of 2 with Michael acceptors, 2,3-dihydrofuran and 2H-3,4-dihydro-pyran, in 57 and 59% yields, respectively. The structures of 1d—f were determined by ultraviolet (UV) spectrometry. Namely, it is known that UV absorption maxima of 3-substituted benzoazoline-2-thiones (1) appear in the region of 309 nm and that UV spectra of 2-substituted benzoazoles (3) give two absorption maxima in the regions of 280 and 290 nm (Table 1).

Method B involves an alkylation process of benzoazoline-2-ones (4) to give 3-alkylbenzoazolin-2-ones (5). It is known that the reaction of 4 with alkylating agents, such as alkyl halides,\(^{9}\) dialkyl oxalates,\(^{10}\) dialkyl sulfates,\(^{11}\) or alkyl toluenesulfonates,\(^{12}\) gives 5. However, in our present experiment, these procedures did not give a satisfactory yield of 5 having a long carbon chain at position 3. We succeeded in the synthesis of 5 having such an alkyl group at position 3 by heating a mixture of 4 and 2-alkyl-1,3-dicyclohexylisourea. The resulting 5 was converted to 1 by heating with phosphorus pentasulfide in a mixture of xylene and hexamethylphosphorus triamide (HMPT).

Method C involves an alkylation process of 2-aminophenol to give 2-(alkylamino)phenols (7). Compound 6 was prepared by the reaction of the Schiff base, formed from 2-aminophenol and aldehydes, with sodium borohydride (\(\text{NaBH}_4\)); it was immediately converted to 1 by reaction with potassium \(O\)-methylthiocarbonate because of its instability in air.

Although these three methods seemed to be equally applicable to the preparation of 1 with various substituents at position 3, each of these methods was found to have defects. For example, 3-furfurylbenzoazoline-2-thione (1g) could not be prepared by methods A and B but was obtained in 41% yield by method C: on heating of 2-(furfurylthio)benzoxazole (3g) at 180°C in the presence of small pieces of iodine (method A), rearrangement of the furyl group did not occur and polymeric products were obtained. In method B, the yields of 3-furfurylbenzoazolin-2-one (5g) in the reactions of 4 with furfuryl alcohol and dicyclohexyl-
TABLE 1. UV Data for 1 and 3

<table>
<thead>
<tr>
<th>R</th>
<th>1 (log ε)</th>
<th>2 (log ε)</th>
<th>3 (log ε)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a CH₂⁻</td>
<td>309 (4.48)</td>
<td>280 (4.13)</td>
<td>288 (4.12)</td>
</tr>
<tr>
<td>b tert-C₆H₅⁻</td>
<td>308 (4.45)</td>
<td>281 (4.03)</td>
<td>288 (4.05)</td>
</tr>
<tr>
<td>c C₆H₅CH₂⁻</td>
<td>309 (4.50)</td>
<td>282 (4.21)</td>
<td>289 (4.21)</td>
</tr>
<tr>
<td>d</td>
<td>302 (4.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>304 (4.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>303 (4.46)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

carbodiimide (DCC) or with furfuryl chloride were poor (5%). For another example, rearrangement of the hexyl group of 2-(1-hexylthio)benzoxazole (3h), prepared from 3 and 1-hexyl chloride (method A), did not succeed and the starting material was recovered. Moreover, the preparation of 3-(1-hexyl)benzoxazoline-2-thione (1h) by method C failed. However, 1c was obtained by method B in 50% yield.

In summary, the applicability of method A was found to be limited to the preparation of special analogs of 1 with a substituent such as methyl or benzyl at position 3, which could readily rearrange. Method B was better for the preparation of most analogs of 1 with a few exceptions, such as 1b. Method C was suitable for the preparation of analogs of 1 with a group sensitive to high temperature (which is required in method A), or analogs of 1 with an aryl-(including heterocyclic ring) methyl group.

**Experimental**

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer. UV spectra were taken with Shimadzu UV-180 spectrometer.

**General Procedure of Method A. A Typical Example:** 3-Benzylbenzoxazoline-2-thione (1c)—ii) 2-(Benzyithio)benzoxazole (3c) was prepared by the following methods (a and b). Method a: A solution of benzyl alcohol (5 g), DCC (10 g), and CuCl₂ (a catalytic amount) in dimethylformamide (DMF) (100 ml) was stirred at room temperature overnight. Benzoxazoline-2-thione¹⁰ (2, 7 g) was then added to the solution and the mixture was stirred at room temperature for 1 h. The filtrate was concentrated and the residue was chromatographed on a column of alumina with cyclohexane to give 8 g (72%) of 3c, mp 47—48°C (lit.,¹⁰ 51—52°C).

Method b: A solution of 2 (4 g), benzyl chloride (5 g), and K₂CO₃ (6 g) in DMF (100 ml) was stirred at room temperature for 1 h. The filtrate was concentrated and the residue was chromatographed on a column of alumina with cyclohexane to give 4.8 g (75%) of 3c, which was identical with the authentic sample prepared by method a.

ii) Compound 3c was heated at 180°C for 12 h in the presence of small pieces of iodine and the resulting product was recrystallized from benzene to give 1.2 g (60%) of 1c, mp 167—169.5°C. Anal. Calcd for C₁₃H₁₁NOS: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.83; H, 4.59; N, 5.58. NMR (CDCl₃) δ: 5.46 (2H, s, CH₂). MS m/z: 241 (M⁺).
Similarly, 3-methylbenzoxazole-2-thione (Ia) was prepared from 2-(methylthio)benzoxazole (3a) in 53% yield.  

**General Procedure of Method B. A Typical Example:** 1a—i) 3-Benzylbenzoxazole-2-one (5c) was prepared by the following methods (a and b). Method a: A mixture of benzyl alcohol (3.2 g), DCC (4.9 g), CuCl₂ (a catalytic amount), and dry tetrahydrofuran (THF) (50 ml) was stirred at room temperature overnight, then benzoxazole-2-one (4) (4 g) was added and the solvent was evaporated off. The residue was further heated at 150°C for 6 h and dissolved in CH₃Cl₂. The CH₃Cl₂ layer was washed with 10% KOH and H₂O, dried, and concentrated. The residue was recrystallized from benzene to give 5.2 g (78%) of 5c, mp 130°C (lit. 127°C).  

Method b: Benzyl chloride (2 g) was added to a mixture of 4 (2 g), K₂CO₃ (2 g), and DMF (100 ml). The mixture was then heated at 60°C for 2.5 h and poured into ice-water. The resulting precipitate was recrystallized to give 2.6 g (78%) of 5a, mp 128—130°C, which was identical with the authentic sample prepared by method a.  

Similarly, 3-(1-hexyl)benzoxazole-2-one (5h) was prepared in 54% yield, as an oil, bp 155—160°C (1—2 mmHg). Anal. Calcd for C₁₉H₁₅NO: C, 70.70; H, 7.82; N, 6.39. Found: C, 70.82; H, 8.07; N, 6.13. NMR (CDCl₃) δ: 0.74—2.09 [11H, m, (CH₃)₂CH₂], 3.25 (2H, t, J = 7 Hz, NCH₂). MS m/e: 219 (M⁺).  

ii) A solution of 5c (0.67 g) and P₂S₅ (1.4 g) in HMPT (15 ml) was heated at 120°C for 6 h and poured into NH₃ aq. (50 ml). The mixture was extracted with EtO and the EtO layer was washed with H₂O, dried over MgSO₄, and concentrated. The residue was recrystallized from benzene to give 0.38 g (53%) of 1c, mp 167—169°C, which was identical with an authentic sample.  

Similarly, 3-(1-hexyl)benzoxazole-2-thione (5h) was prepared in 50% yield, mp 66—68°C (from cyclohexane). Anal. Calcd for C₁₉H₁₅NO: C, 66.34; H, 7.28; N, 5.95. Found: C, 65.85; H, 7.40; N, 5.72. NMR (CDCl₃) δ: 0.64—2.13 [11H, m, (CH₃)₂CH₂], 3.82 (2H, t, J = 7 Hz, NCH₂). MS m/e: 235 (M⁺).  

**General Procedure of Method C. A Typical Example:** 1a—2-Aminophenol (3 g) was added portionwise to a mixture of benzaldehyde (3.6 g) and methanol (180 ml). The mixture was stirred at room temperature overnight, then NaBH₄ (2.1 g) was gradually added with cooling. The mixture had been stirred at room temperature for 0.5 h, Cs₂O (10 g) was added. The solution was then allowed to reflux for 30 h and poured into ice-water. The resulting precipitate was washed with 10% HCl and recrystallized from cyclohexane to give 5.5 g (81%) of 1c, which was identical with an authentic sample.  

Similarly, 3-furfuryl (1g), 3-[4-N,N-dimethylamino benzyl]- (1k), 3-[2,4-dimethoxybenzyl]- (1m), and 5-chloro-3-[2-thienylmethyl]- (1m) benzoxazole-2-thiones were prepared. 1g: Yield 41%. mp 103—105.5°C (from benzene—cyclohexane). Anal. Calcd for C₁₉H₁₇NO: C, 62.34; H, 3.92; N, 5.06. Found: C, 62.18; H, 3.80; N, 5.88. NMR (CDCl₃) δ: 3.58 (2H, s, NCH₂). MS m/e: 231 (M⁺).  

1k: Yield 42%. mp 159—161°C (from THF—MeOH). Anal. Calcd for C₂₃H₂₃N₂O: C, 76.57; H, 5.67; N, 9.85. Found: C, 76.27; H, 5.55; N, 9.64. NMR (DMSO-d₆) δ: 2.89 (6H, s, CH₃x2), 5.40 (2H, s, NCH₂). MS m/e: 284 (M⁺).  

1m: Yield, 99%. mp 134—135°C (from benzene—cyclohexane). Anal. Calcd for C₂₃H₂₄N₂O: C, 63.77; H, 5.01; N, 4.65. Found: C, 64.13; H, 4.90; N, 4.45. NMR (DMSO-d₆) δ: 3.75 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 5.37 (2H, s, NCH₂). MS m/e: 301 (M⁺).  

3-(1-Isocromanyl)benzoxazole-2-thione (1d)—A solution of 2 (4.5 g) and 1-ethoxyisochromanogen (7 g) in xylene (50 ml) was allowed to reflux for 1 h in an Ar atmosphere while the xylene and the EtOH formed were distilled off. The xylene was then completely removed under reduced pressure and the residue was recrystallized from AcOEt—petr. ether (1: 2) to give 7.1 g (85%) of 1d, mp 126—126.5°C. Anal. Calcd for C₂₃H₂₀NO: C, 76.84; H, 4.63; N, 4.95. Found: C, 75.84; H, 4.52; N, 4.78. NMR (CDCl₃) δ: 2.60—3.53 (2H, m, C₃H₃), 3.38—4.40 (2H, m, C₃H₃). MS m/e: 283 (M⁺).  

3-(2-Tetrahydrofuryl)benzoxazole-2-thione (1e)—Method a: A solution of 2 (2 g) and 2-ethoxytetrahydrofuran (4.5 g) in xylene (150 ml) was heated at 150°C for 36 h in an autoclave, then concentrated. The residue was chromatographed on a column of alumina with AcOEt—petr. ether (1: 15) to give 2.2 g (79%) of 1e, mp 56—58°C. Anal. Calcd for C₁₉H₁₇NO: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.39; H, 5.60; N, 6.01. NMR (CDCl₃) δ: 1.42—2.20 (6H, m, C₃H₃, C₃H₂, and C₃H₂), 3.44—4.43 (2H, m, C₃H₃), 5.89—6.35 (1H, m, C₃H₂). MS m/e: 235 (M⁺).  

Method b: A solution of 2 (2 g) and 2H-3,4-dihydrofuran (3.3 g) in pyridine (80 ml) was heated at 150°C for 12 h in an autoclave, then concentrated. The residue was chromatographed on a column of alumina
with AcOEt–petr. ether (1:15) to give 1.8 g (59%) of 1f as a viscous oil, which was identical with the authentic sample prepared by method a.

**Reaction of 2 with tert-Butyl Bromide**—tert-Butyl bromide (10 g) was added to a mixture of 2 (5 g), K$_2$CO$_3$ (10 g), and dry DMF (100 ml) with cooling. The mixture was heated at 60°C for 12 h, poured into ice-water, and extracted with Et$_2$O. The Et$_2$O layer was washed with H$_2$O, dried, and concentrated. The residue was chromatographed on a column of alumina. Elution with cyclohexane gave 0.32 g (5%) of 2-(tert-butylthio)benzoxazole$^7$ (3b). Further elution with benzene gave 1.32 g (19%) of 3-tert-butylbenzoxazole-2-thione (1b), mp 129–132°C (from cyclohexane). *Anal.* Calcd for C$_{12}$H$_{14}$NOS: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.91; H, 6.49; N, 6.80. NMR (CDCl$_3$) δ: 2.04 (9H, s, CH$_3$ × 3), 7.08–7.87 (4H, m, aromatic H). MS m/e: 207 (M$^+$).

**References and Notes**