SYNTHESIS OF 2-(2-ALKOXYCARBONYLPHENYLTHIO)-1,2-BENZISOTHIAZOLIN-3-ONES FROM 2-SULFENAMOYL BENZOATES

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Abstract—The Mechanism of formation of 2-(2-alkoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones, which were obtained by the heating of 2-sulfenamoylbenzoates, was investigated. It appears that transamination occurred on the sulfur atom of a 2-sulfenamoylbenzoate between the amino group and the 1,2-benzisothiazolin-3-one, which formed by the cyclization of methyl 2-sulfenamoylbenzoate after heating, to give 2-(2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones. Several types of 2-sulfenyl-1,2-benzisothiazolin-3-ones were synthesized from the 2-sulfenamoylbenzoates.

1,2-Benzisothiazolin-3-ones have been reported to possess high antibacterial and antifungal activity, and their derivatives have also shown various kinds of bioactive properties. For examples, 2-sulfenyl-1,2-benzisothiazolin-3-ones have been used as bactericides and fungicides or as anticytotoxic agents. These 2-sulfenyl-1,2-benzisothiazolin-3-ones were synthesized from the reaction of 1,2-benzisothiazolin-3-ones with sulfenyl chlorides that were usually prepared from treatment of the corresponding disulfides or thiols with chlorine. Since chlorine is a hazardous, poisonous, and corrosive gas, a chlorine-free procedure for the synthesis of 2-sulfenyl-1,2-benzisothiazolin-3-ones is strongly desired. In a preceding paper, we reported a facile method for the synthesis of 1,2-benzisothiazolin-3-ones from thiosalicylates. 1,2-Benzisothiazolin-3-ones have been synthesized mainly from the reaction of amines with sulfenyl chloride derivatives of thiosalicylic acid. According to our new method, 2-sulfenamoylbenzoates (1), which were prepared from the
reaction of thiosalicylates with hydroxylamine-O-sulfonic acid, cyclized to form 1,2-benzisothiazolin-3-ones under basic conditions at room temperature, and chlorine-free synthesis of 1,2-benzisothiazoline-3-ones was accomplished. However, during the investigation of optimum cyclization conditions, we found that an unexpected product, 2-(2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3a), was formed as a major product when the cyclization of methyl 2-sulfenamoylbenzoate (1a) was carried out at 100 °C in the absence of base (Scheme 1). In this paper, we describe the reaction mechanism and synthesis of various 2-(2-alkoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones.

RESULTS AND DISCUSSION
As reported in the preceding paper, methyl 2-sulfenamoylbenzoate (1a) formed 3a when heated at 100 °C in toluene. When the reaction was carried out with a decreased amount of solvent, the yield of 3a improved (Entry 1) (see Table 1). Although methyl 5-chloro-2-sulfenamoylbenzoate (1b) afforded the corresponding 3b, the yield was low because a large amount of slightly soluble 5-chloro-1,2-benzisothiazolin-3-one (2b) was formed (Entry 2). In the case of the ethyl ester (1c), cyclization did not occur at 100 °C, and the starting 1c was recovered (Entry 3).

It has already been shown that N-2-methoxycarbonylphenylthio-2-methoxycarbonylbenzenesulfenamide (4), which was isolated as a by-product when 1a was heated, does not cyclize to 3a at 100 °C, and that there must be another reaction path for the formation of 3a. It has been reported that ammonia may be eliminated by treating 2-sulfenamoylbenzothiazoles with primary or secondary amines, thereby forming N-mono- or N,N-disubstituted sulfenamides, respectively. Therefore, it is expected that a similar transamination occurred in the case of the sulfenamide 1a: the amino group of the sulfenamide was replaced with 1,2-benzisothiazolin-3-one (2a) to give 3a. When ethyl 2-
sulfenamoylbenzoate (1c), which did not afford 3 when heated in toluene at 100 °C, was heated in toluene with 1,2-benzisothiazolin-3-one (2a) at 100 °C, 3c was isolated in good yield (Entry 4), indicating that transamination occurred between 1,2-benzisothiazolin-3-one and the amino group of the sulfenamide.

From these results, it appears that the mechanism of formation of 3a from methyl 2-sulfenamoylbenzoate (1a) is as follows (Scheme 2). When 1a was heated at 100 °C,

methanol was eliminated to form cyclized 1,2-benzisothiazolin-3-one (2a). The 1,2-benzisothiazolin-3-one attacked the sulfur atom of the sulfenamide, and ammonia was eliminated; as a result, 3a was formed. In the same manner, 4 was formed when ammonia was eliminated from two molecules of 1a. On the basis of this mechanism, various kinds of

![Scheme 2](image)

Table 1. Synthesis of 2-sulfenyl-1,2-benzisothiazolin-3-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfenamide</th>
<th>R¹</th>
<th>R²</th>
<th>Y</th>
<th>Method ¹</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>Me</td>
<td>CH</td>
<td>A</td>
<td>3a</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Cl</td>
<td>Me</td>
<td>CH</td>
<td>A</td>
<td>3b</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>H</td>
<td>Et</td>
<td>CH</td>
<td>A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>H</td>
<td>Et</td>
<td>CH</td>
<td>B</td>
<td>3c</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>H</td>
<td>i-Pr</td>
<td>CH</td>
<td>B</td>
<td>3d</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>1e</td>
<td>H</td>
<td>Et</td>
<td>N</td>
<td>B</td>
<td>3e</td>
<td>40</td>
</tr>
</tbody>
</table>

¹ Method A: 1, 2 mmol; toluene, 10 mL; 100 °C; 5 h.
Method B: 1, 1 mmol; 2, 1 mmol; toluene, 10 mL; 100 °C; 5 h.
2-sulfenyl-1,2-benzisothiazolin-3-ones were synthesized using two methods (Table 1): by heating various methyl 2-sulfenamoylbenzoates and by the reaction of the 2-sulfenamoylbenzoates with 1,2-benzisothiazolin-3-one.

In conclusion, the reaction described here, in which the amino group in several 2-sulfenamoylbenzoates was easily replaced with various 1,2-benzisothiazolin-3-ones, provide a chlorine-free method for the synthesis of 2-(2-alkoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones.

EXPERIMENTAL

Melting points were determined on a Mettler FP90 microscope plate, and uncorrected. $^1$H-NMR spectra were obtained with a Varian Gemini 300 BB spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer.

**Synthesis of 2-(2-alkoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones (3).**

**Method A: Heating of methyl 2-sulfenamoylbenzoates.**

Methyl 2-sulfenamoylbenzoates (1, 2 mmol) was dissolved in toluene (10 mL), and the solution was heated at 100 °C for 5 h. After evaporating of toluene, the residual crude product was chromatographed on silica gel with dichloromethane-acetone-methanol (100:5:1) mixture as an eluent. The product was recrystallized from benzene-hexane mixture.

**Method B: Reaction of sulfenamides with 1,2-benzisothiazolin-3-one.**

2-Sulfenamoylbenzoates (1, 1 mmol) and 1,2-benzisothiazolin-3-one (2a, 151 mg, 1 mmol) were dissolved in toluene (10 mL), and the solution was heated at 100 °C for 5 h. After evaporating of toluene, the residual crude product was chromatographed on silica gel with dichloromethane-acetone-methanol (100:5:1) mixture as an eluent. The product was recrystallized from benzene-hexane mixture.

2-(2-Methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3a).$^5$

mp 187.5-189 °C; $^1$H-NMR (CDCl$_3$) $\delta$ 3.98 (3H, s), 6.83 (1H, d, $J=8.2$ Hz), 7.24 (1H, dd, $J=8.8, 8.0$ Hz), 7.40-7.47 (2H, m), 7.58 (1H, dd, $J=8.2$ Hz), 7.71 (1H, td, $J=8.2, 1.1$ Hz), 8.06 (1H, dd, $J=8.8, 1.1$ Hz), 8.14 (1H, dd, $J=8.0, 1.4$ Hz); IR (KBr) $\nu_{\text{max}}$ 1688, 1318, 1281, 1107,
5-Chloro-2-(4-chloro-2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3b).
mp 193-194 °C; \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \) 3.99 (3H, s), 6.72 (1H, dd, \( J = 8.8, 1.1 \) Hz), 7.39 (1H, dt, \( J = 8.8, 2.0 \) Hz), 7.52 (1H, dd, \( J = 8.8, 0.6 \) Hz), 7.66-7.69 (1H, m), 8.04 (1H, t, \( J = 2.2 \) Hz), 8.10 (1H, t, \( J = 2.2 \) Hz); IR (KBr) \( \nu_{max} \) 1703, 1669, 1449, 1308, 1252, 1123 cm\(^{-1}\); Anal. Calcd for C\(_{15}\)H\(_{11}\)NO\(_3\)S\(_2\): C, 56.76; H, 3.49; N, 4.41. Found: C, 56.69; H, 3.42; N, 4.36.

2-(2-Ethoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3c).
mp 169-171 °C; \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \) 1.44 (3H, t, \( J = 7.1 \) Hz), 4.45 (2H, q, \( J = 7.1 \) Hz), 6.82 (1H, dd, \( J = 8.2, 0.8 \) Hz), 7.24 (1H, td, \( J = 8.0, 1.1 \) Hz), 7.40-7.48 (2H, m), 7.57 (1H, d, \( J = 8.0 \) Hz), 7.71 (1H, td, \( J = 8.0, 0.8 \) Hz), 8.08 (1H, dd, \( J = 8.0, 0.8 \) Hz), 8.14 (1H, dd, \( J = 8.0, 0.8 \) Hz); IR (KBr) \( \nu_{max} \) 1686, 1281, 1103, 752, 731 cm\(^{-1}\); Anal. Calcd for C\(_{16}\)H\(_{13}\)NO\(_3\)S\(_2\): C, 57.99; H, 3.95; N, 4.23. Found: C, 57.86; H, 3.89; N, 4.04.

2-(2-Isopropoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3d).
mp 163-164.5 °C; \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \) 1.41 (6H, d, \( J = 6.3 \) Hz), 5.31 (1H, sep, \( J = 6.3 \) Hz), 6.81 (1H, dd, \( J = 8.2, 0.8 \) Hz), 7.23 (1H, td, \( J = 7.4, 1.1 \) Hz), 7.39-7.47 (2H, m), 7.57 (1H, d, \( J = 8.2 \) Hz), 7.71 (1H, td, \( J = 7.4, 1.1 \) Hz), 8.07 (1H, dd, \( J = 8.0, 1.1 \) Hz), 8.14 (1H, dd, \( J = 7.4, 1.4 \) Hz); IR (KBr) \( \nu_{max} \) 1667, 1283, 1098, 737 cm\(^{-1}\); Anal. Calcd for C\(_{17}\)H\(_{15}\)NO\(_3\)S\(_2\): C, 59.11; H, 4.38; N, 4.05. Found: C, 59.27; H, 4.33; N, 3.90.

2-(3-Ethoxycarbonyl-2-pyridylthio)-1,2-benzisothiazolin-3-one (3e).
mp 169-171 °C; \( ^1H \)-NMR (CDCl\(_3\)) \( \delta \) 1.45 (3H, t, \( J = 7.1 \) Hz), 4.47 (2H, q, \( J = 7.1 \) Hz), 7.13 (1H, dd, \( J = 8.0, 4.8 \) Hz), 7.41 (1H, td, \( J = 7.4, 0.8 \) Hz), 7.53 (1H, dd, \( J = 7.4, 0.8 \) Hz), 7.68 (1H, td, \( J = 7.1, 1.4 \) Hz), 8.12 (1H, dt, \( J = 8.0, 0.8 \) Hz), 8.26 (1H, dd, \( J = 7.7, 1.9 \) Hz), 8.43 (dd, 1H, \( J = 4.8, 1.9 \) Hz); IR (KBr) \( \nu_{max} \) 1696, 1680, 1298, 1154, 1113, 1071, 737 cm\(^{-1}\); Anal. Calcd for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_3\)S\(_2\): C, 54.20; H, 3.64; N, 8.43. Found: C, 54.25; H, 3.65; N, 8.34.

REFERENCES


