

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

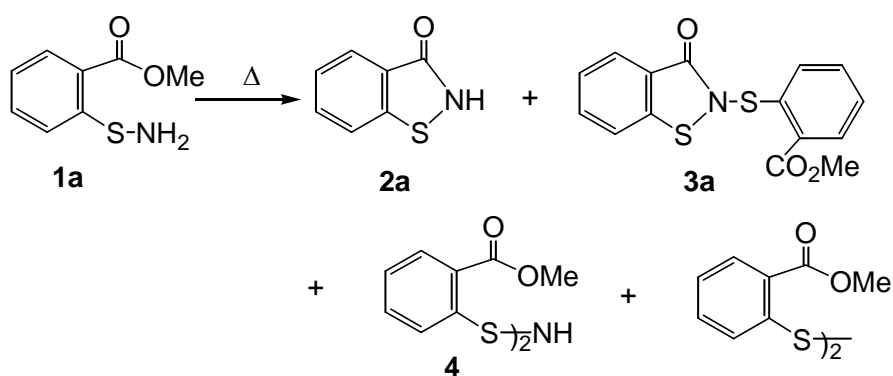
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Abstract—The Mechanism of formation of 2-(2-alkoxycarbonylphenylthio)-1,2-benzisothiazolin-3-ones, which were obtained by the heating of 2-sulfenamoylbenzoates, was investigated. It appears that transamination occurred on the sulfur atom of a 2-sulfenamoylbenzoate 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,¹ and their derivatives have also shown various kinds of bioactive properties.² For examples, 2-sulfenyl-1,2-benzisothiazolin-3-ones have been used as bactericides and fungicides³ or as anticryptogamic agents.⁴ These 2-sulfenyl-1,2-benzisothiazolin-3-ones^{3,4} 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.⁵ 1,2-Benzisothiazolin-3-ones have been synthesized mainly from the reaction of amines with sulfenyl chloride derivatives of thiosalicylic acid.⁶ 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.



Scheme 1

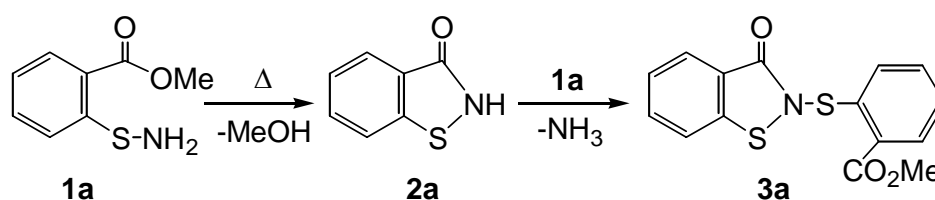
RESULTS AND DISCUSSION

As reported in the preceding paper, methyl 2-sulfenamoylbenzoate (**1a**) formed **3a** when heated at 100 °C in toluene.⁵ 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**.⁵ 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.⁷ 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,



Scheme 2

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

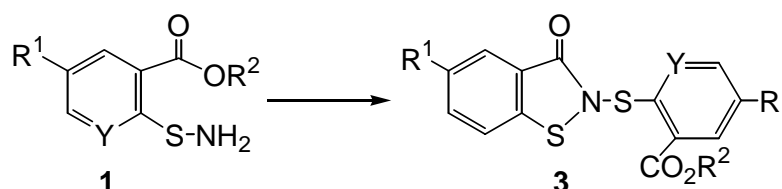


Table 1. Synthesis of 2-sulphenyl-1,2-benzisothiazolin-3-ones

| Entry | Sulfenamide | R ¹ | R ² | Y | Method ^a | Product | Yield (%) |
|-------|-------------|----------------|----------------|----|---------------------|-----------|-----------|
| 1 | 1a | H | Me | CH | A | 3a | 90 |
| 2 | 1b | Cl | Me | CH | A | 3b | 29 |
| 3 | 1c | H | Et | CH | A | - | - |
| 4 | 1c | H | Et | CH | B | 3c | 66 |
| 5 | 1d | H | <i>i</i> -Pr | CH | B | 3d | 52 |
| 6 | 1e | H | Et | N | B | 3e | 40 |

^a 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. ¹H-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; ¹H-NMR (CDCl₃) δ 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) ν_{max} 1688, 1318, 1281, 1107,

733 cm^{-1} ; *Anal.* Calcd for $\text{C}_{15}\text{H}_{11}\text{NO}_3\text{S}_2$: C, 56.76; H, 3.49; N, 4.41. Found: C, 56.69; H, 3.42; N, 4.36.

5-Chloro-2-(4-chloro-2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3b).

mp 193-194 $^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 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) ν_{max} 1703, 1669, 1449, 1308, 1252, 1123 cm^{-1} ; *Anal.* Calcd for $\text{C}_{15}\text{H}_9\text{NO}_3\text{Cl}_2\text{S}_2$: C, 46.64; H, 2.35; N, 3.63. Found: C, 46.95; H, 2.31; N, 3.50.

2-(2-Ethoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (3c).

mp 169-171 $^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 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) ν_{max} 1686, 1281, 1103, 752, 731 cm^{-1} ; *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_3\text{S}_2$: 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 $^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 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) ν_{max} 1667, 1283, 1098, 737 cm^{-1} ; *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_3\text{S}_2$: 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 $^{\circ}\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 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) ν_{max} 1696, 1680, 1298, 1154, 1113, 1071, 737 cm^{-1} ; *Anal.* Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3\text{S}_2$: C, 54.20; H, 3.64; N, 8.43. Found: C, 54.25; H, 3.65; N, 8.30.

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