HETEROCYCLES, Vol. 53, No12, 2000, pp. 2803 - 2808, Received, 25th August, 2000

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

Masao Shimizu,* Toshiyuki Takagi, Motonari Shibakami, Yasuo Gama, and Isao Shibuya

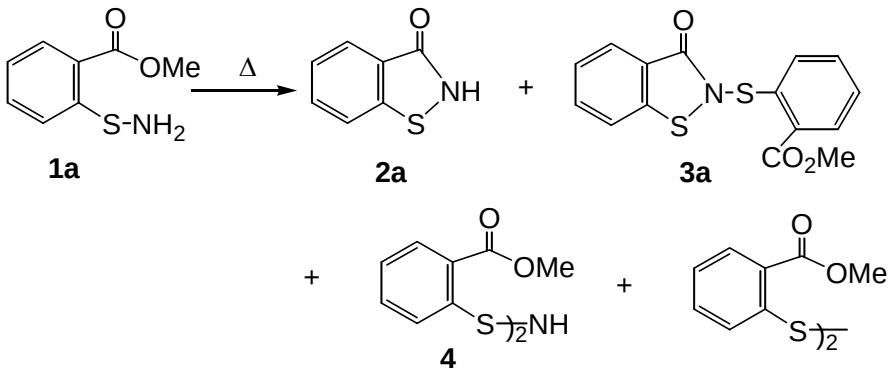
National Institute of Material and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

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 fungicides[3] 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 wer 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

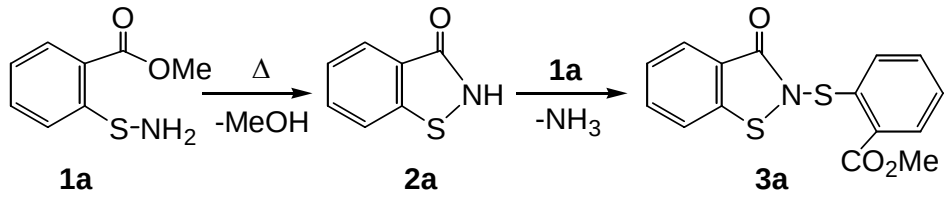
RESULTS AND DISCUSSION

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-methoxycarbonyl-benzenesulfenamide (**4**), which was isolated as a by-product when **1a** was hearted, 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

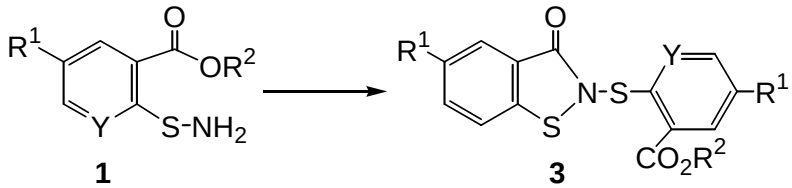


Table 1. Synthesis of 2-sulfenyl-1,2-benzisothiazolin-3-ones

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*-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. ^{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 ($CDCl_3$) 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 $C_{15}H_{11}NO_3S_2$: 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 °C; ^{1}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 $C_{15}H_9NO_3Cl_2S_2$: 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 °C; ^{1}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 $C_{16}H_{13}NO_3S_2$: 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; ^{1}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 $C_{17}H_{15}NO_3S_2$: 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; ^{1}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 $C_{15}H_{12}N_2O_3S_2$: C, 54.20; H, 3.64; N, 8.43. Found: C, 54.25; H, 3.65; N, 8.30.

REFERENCES

1. a) M. Davis, *Adv. Heterocycl. Chem.*, 1972, **14**, 58; b) J. C. Grivas, *Ger. Offen.*, 2,119,730 (1971) (*Chem. Abstr.*, 1972, **76**, 46193); c) R.Fischer and H. Hurni, *Arzneimittel-Forsch.*, 1964, **14**, 1301 (*Chem. Abstr.*, 1965, **63**, 13728); d) F. Gialdi, R. Ponci, A. Baruffini, and P. Borgna, *Farmaco, Ed. Sci.*, 1964, **19**, 76 (*Chem. Abstr.*, 1964, **60**, 9266); e) J. S. Morley, *Brit. Patent*, 848,130 (1960) (*Chem. Abstr.*, 1961, **55**, 9430);f)

Z. Eckstein and E. Zukowski, *Przemysl Chem.*, 1958, **37**, 418 (*Chem. Abstr.*, 1959, 53, 5246).

2. D. L. Pain, B. J. Peart, and K. R. H. Wooldridge, 'Comprehensive Heterocyclic Chemistry,' Vol. 6, ed. by K. T. Potts, Pergamon Press, Oxford, 1984, p. 175.
3. a) A. J. Buckley, E. G. Gazzard, M. Singer, and J. A. Taylor, *Ger. Offen.*, 2,419,017 (1974) (*Chem. Abstr.*, 1975, **82**, 72979); b) R. Ponci, A. Baruffini, and P. Borgna, *Farmaco, Ed. Sci.*, 1966, **21**, 249 (*Chem. Abstr.*, 1967, **66**, 37816).
4. A. Baruffini, F. Gialdi, and R. Ponci, *Fr. Patent*, 1,411,720 (1965) (*Chem. Abstr.*, 1966, **64**, 2092).
5. M. Shimizu, H. Kikumoto, T. Konakahara, Y. Gama, and I. Shibuya, *Heterocycles*, 1999, **51**, 3005.
6. a) E. W. McClelland and A. J. Gait, *J. Chem. Soc.*, **1926**, 921; b)M. Davis, *Adv. Heterocycl. Chem.*, 1972, **14**, 58.
7. a) E. L. Carr, G. E. P. Smith, Jr., and G. Alliger, *J. Org. Chem.*, 1949, **14**, 921; b) M. J. Gattuso, *US Patent*, 4,041,043 (1977) (*Chem. Abstr.*, 1977, **87**, 137106); c) L. H. Howland, *US Patent*, 2,382,793 (1945) (*Chem. Abstr.*, 1948, **40**, 368).