A FACILE SYNTHESIS OF 1,2-BENZISOTHIAZOLIN-3-ONES FROM THIOSALICYLATES

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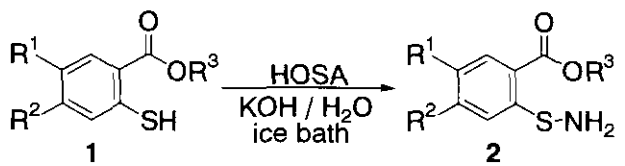
Abstract – Synthesis of 1,2-benzisothiazolin-3-ones by cyclization of 2-sulfenamoylbenzoates, which were prepared from amination of thiosalicylates by hydroxylamine-*O*-sulfonic acid, was examined. Although treatment of methyl 2-sulfenamoylbenzoate on heating gave unexpected 2-(2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one, the treatment with base at room temperature afforded 1,2-benzisothiazolin-3-one in a good yield.

Synthesis of 1,2-benzisothiazolin-3-ones and their derivatives is of wide spread interest due to their potential as pharmaceuticals.[1] For example, 5-chloro- and 6-chloro-1,2-benzisothiazolin-3-ones have efficient antifungal and antibacterial properties.[2] It was reported that 1-(1,2-benzisothiazol-3-yl)piperazine derivatives which were prepared from 1,2-benzisothiazolin-3-one showed potential antipsychotic properties.[3] Furthermore, oxidation of 1,2-benzisothiazolin-3-one afforded 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin),[4] which is well-known as a sweetening agent. In the literature, *N*-unsubstituted 1,2-benzisothiazolin-3-ones were synthesized from the reaction of ammonia with sulfenyl halide derivatives of thiosalicylic acid,[5] or from the reaction of ammonia with 3*H*-1,2-benzodithiol-3-one[4a] or 3*H*-1,2-benzothiol-3-one 1-oxide.[6] The former synthetic

method is not convenient especially for laboratory use because the use of toxic chlorine gas is necessary for preparing sulfenyl chlorides, and in some cases two equivalents of the sulfenyl chloride reacted with ammonia.[7] Since it was reported that β-sulfenamoyl carbonyl compounds were cyclized to isothiazole rings,[8] we developed a facile synthetic method of 1,2-benzisothiazolin-3-ones from the cyclization of 2-sulfenamoylbenzoates.

RESULTS AND DISCUSSION

2-Sulfenamoylbenzoates (2) were synthesized from amination of thiosalicylates (1). When an aqueous solution of hydroxylamine-*O*-sulfonic acid (HOSA) with an equimolecular amount of potassium hydroxide was added dropwise to an aqueous solution of methyl thiosalicylate (1a) and potassium hydroxide on an ice bath, white crystalline began to precipitate. The product was methyl 2-sulfenamoylbenzoate (2a) which underwent amination at the mercapto group of 1a. The same treatment for various kinds of thiosalycilates with HOSA gave 2-sulfenamoylbenzoates, and the results are shown in Table 1.



1 2

Scheme 1

Table 1. Synthesis of 2-sulfenamoylbenzoates (2).[a]

Thiosalicylate	R^1	R^2	R^3	Product	Yield[b] / %
1a	H	H	Me	2a	68
1b	H	H	Et	2b	98
1c	H	Cl	Me	2c	73
1d	Cl	H	Me	2d	70
1e	MeO	MeO	Me	2e	89

[a] 1, 2 mmol; HOSA, 3 mmol; KOH, 5 mmol; H_2O, 40 mL; ice bath; 30 min.
[b] Isolated yield.

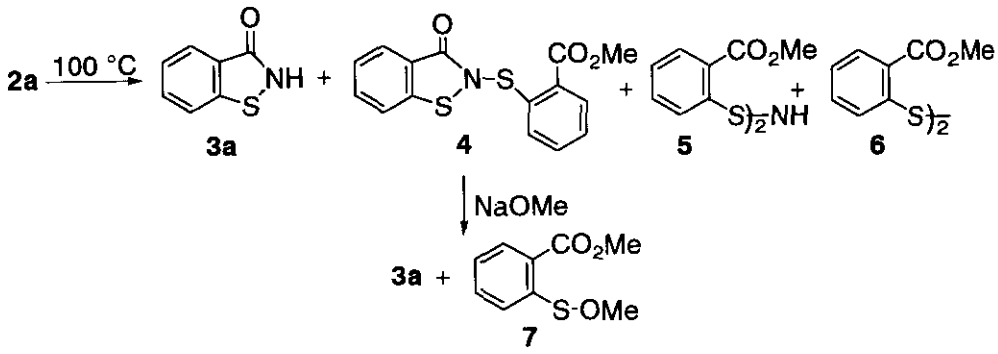
Cyclization of the isolated sulfenamoylbenzoates (2) was examined to synthesize 1,2-benzisothiazolin-3-ones (3) (Table 2). First, intramolecular removal of methanol from 2a

Table 2. Cyclization of methyl 2-sulfenamoylbenzoate (2a).[a]

Run	Solvent	Base	Temp.	Time / h	Yield[b] / %				
					3a	4	5	6	7
1	toluene	-	100 °C	5	23	58	5	13	-
2	MeOH	NaOMe	reflux	3	28	19	-	-	24
3	MeOH	KOH	rt	0.5	50	-	-	-	-
4	EtOH	NaOH	rt	0.5	80	-	-	-	-
5	EtOH	KOH	rt	0.5	87	-	-	-	-

[a] 2a, 1 mmol; base 1 mmol; solvent, 20 mL.
[b] Isolated yield.

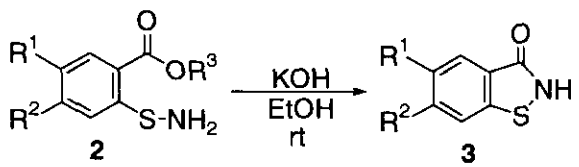
was tried on heating (Run 1). When 2a was heated at 100 °C in toluene for 5 h, 1,2-benzisothiazolin-3-one (3a) was obtained in 23% yield, but a main product was the compound (4) showing a molecular formula $C_{15}H_{11}NO_3S_2$. In this reaction, *N*-2-methoxycarbonylphenylthio-2-methoxycarbonylbenzenesulfenamide (5) and bis(2-methoxycarbonylphenyl)sulfide (6) were also formed as by-products. When the main product (4) was treated with sodium methoxide in methanol, 3a and methyl 2-methoxycarbonylbenzenesulfenate (7) were obtained in 34 and 71% yields, respectively. From these results and ^{1}H NMR spectral data, the structure of 4 was determined as 2-(2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (Scheme 2). It seemed that 4 was formed by way of cyclization of 5. However, treatment of 5 in toluene at 100 °C did not afford 4, and 5 was recovered. Therefore, there was another reaction path for the formation of 4.



Scheme 2

Next, cyclization reaction of 2a was tried in alcohol under basic conditions. When 2a was

refluxed in methanol in the presence of sodium methoxide, the yield of 3a was improved but 4 and 7 were still formed in 19 % and 24 % yields, respectively (Run 2). Therefore, reaction conditions were changed milder than above. As a result, 3a was obtained in good yield in ethanol with sodium or potassium hydroxide at room temperature (Runs 4 and 5). For various 2-sulfenamoylbenzoates (2), cyclizations occurred under these reaction conditions, and the corresponding 1,2-benzisothiazolinones (3) were synthesized in good yields (Table 3).



Scheme 3

Table 3. Synthesis of 1,2-benzisothiazolin-3-ones (3).[a]

Sulfenamide	R^1	R^2	R^3	Product	Yield[b] / %
2a	H	H	Me	3a	87
2b	H	H	Et	3a	69
2c	H	Cl	Me	3c	46
2d	Cl	H	Me	3d	75
2e	MeO	MeO	Me	3e	72

[a] 2, 1 mmol; KOH, 1 mmol; EtOH, 20 mL; rt; 30 min.
[b] Isolated yield.

In conclusion, we have provided a facile and safe method for the synthesis of 1,2-benzisothiazolin-3-ones from thiosalicylates.

EXPERIMENTAL

Melting points were determined on a Mettler FP90 microscope plate, and uncorrected. ^1H and ^{13}C 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.

General procedure for the synthesis of 2-sulfenamoylbenzoates (2).

HOSA (339 mg, 3 mmol) was dissolved in water (20 mL) in which potassium hydroxide (168 mg, 3 mmol) was dissolved. This solution was added dropwise to a solution of thiosalicylate (1, 2 mmol) in water (20 mL) in the presence of potassium hydroxide (112 mg, 2 mmol) on an ice bath under nitrogen atmosphere. After 30 min, precipitated white solid was filtered and dried under reduced pressure. The product was recrystallized from dichloromethane-hexane.

Methyl 2-sulfenamoylbenzoate (2a).

mp 88-89 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (2H, br s), 3.91 (3H, s), 7.15 (1H, t, J=8.1 Hz), 7.56 (1H, t, J=8.1 Hz), 7.94 (1H, d, J=8.1 Hz), 8.01 (1H, d, J=8.1 Hz); IR (KBr) ν_{max} 3391, 3299, 1698, 1269, 739 cm^{-1}; Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.69. Found: C, 52.41; H, 4.91; N, 7.34.

Ethyl 2-sulfenamoylbenzoate (2b).

mp 74-75 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J=7.1 Hz), 2.62 (2H, br s), 4.38 (2H, q, J=7.1 Hz), 7.15 (1H, t, J=8.1 Hz), 7.56 (1H, t, J=8.1 Hz), 7.93 (1H, d, J=8.1 Hz), 8.03 (1H, d, J=8.1 Hz); IR (KBr) ν_{max} 3370, 3281, 1692, 1275, 754 cm^{-1}; Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10. Found: C, 54.57; H, 5.52; N, 6.74.

Methyl 4-chloro-2-sulfenamoylbenzoate (2c).

mp 113-114 °C; ^{1}H NMR ($CDCl_3$) δ 2.64 (2H, br s), 3.91 (3H, s), 7.11 (1H, dd, J=8.2, 2.2 Hz), 7.92 (1H, d, J=8.2 Hz), 8.00 (1H, d, J=2.2 Hz); IR (KBr) ν_{max} 3366, 3291, 1705, 1279, 1098, 770 cm^{-1}; Anal. Calcd for $C_8H_8NO_2ClS$: C, 44.14; H, 3.70; N, 6.43. Found: C, 44.31; H, 3.72; N, 6.40.

Methyl 5-chloro-2-sulfenamoylbenzoate (2d).

mp 194 °C (sublimation); ^{1}H NMR ($CDCl_3$) δ 2.62 (2H, br s), 3.92 (3H, s), 7.51 (1H, dd, J=8.8, 2.2 Hz), 7.95 (1H, d, J=8.8 Hz), 7.98 (1H, d, J=2.2 Hz); IR (KBr) ν_{max} 3385, 3297, 1703, 1312, 1244, 820, 781, 523 cm^{-1}; Anal. Calcd for $C_8H_8NO_2ClS$: C, 44.14; H, 3.70; N, 6.43. Found: C, 44.41; H, 3.48; N, 6.10.

Methyl 4,5-dimethoxy-2-sulfenamoylbenzoate (2e).

mp 148-150 °C; ^{1}H NMR ($CDCl_3$) δ 2.67 (2H, br s), 3.89 (3H, s), 3.91 (3H, s), 4.00 (3H, s), 7.49 (1H, s), 7.63 (1H, s); IR (KBr) ν_{max} 3383, 3289, 1690, 1503, 1429, 1263, 1181, 1105, 980, 775 cm^{-1}; Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.36; H, 5.40; N, 5.76. Found: C, 49.21; H, 5.30; N, 5.38.

Reaction of methyl 2-sulfenamoylbenzoate (2a) in toluene.

The solution of methyl 2-sulfenamoylbenzoate (**2a**, 183 mg, 1 mmol) in toluene (20 mL) was stirred for 5 h at 100 °C. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica gel with dichloromethane : hexane (1:1) mixture then dichloromethane : acetone : methanol (100:40:8) mixture as eluent. **3a**, **4**, **5**, and **6** were isolated in 23, 58, 5, and 13 % yields, respectively.

2-(2-Methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (4).

mp 187.5-189 °C (from benzene-hexane); ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 6.83 (1H, d, J=8.2 Hz), 7.24 (1H, t, J=8.2 Hz), 7.40-7.47 (2H, m), 7.57 (1H, d, J=8.2 Hz), 7.71 (1H, t, J=8.2 Hz), 8.06 (1H, d, J=8.2 Hz), 8.13 (1H, d, J=8.2 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.

***N*-2-Methoxycarbonylphenylthio-2-methoxycarbonylbenzenesulfenamide (5).**

mp 202-205 °C (decomp) (lit.,[7] 200-202 °C (decomp), from methanol); ^{1}H-NMR ($CDCl_3$) δ 3.89 (6H, s), 4.19 (1H, s), 7.23 (2H, t, J=8.2 Hz), 7.65 (2H, t, J=8.2 Hz), 7.88 (2H,d, J=8.2 Hz), 8.03 (2H, d, J=8.2 Hz); IR (KBr) ν_{max} 3270, 1707, 1435, 1275, 743 cm^{-1}.

Bis(2-methoxycarbonylphenyl)sulfide (6).

mp 132-132.5 °C (lit.,[7] 131.5-133 °C, from benzene-hexane); ^{1}H-NMR ($CDCl_3$) δ 3.99 (6H, s), 7.24 (2H, t, J=8.2 Hz), 7.42 (2H, t, J=8.2 Hz), 7.76 (2H,d, J=8.2 Hz), 8.07 (2H, d, J=8.2 Hz); IR (KBr) ν_{max} 1707, 1435, 1273, 741 cm^{-1}.

Reaction of 2-(2-methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (4) with sodium methoxide.

2-(2-Methoxycarbonylphenylthio)-1,2-benzisothiazolin-3-one (**4**, 317 mg, 1 mmol) was dissolved in the mixture of methanol (20 mL) and dichloromethane (10 mL), and sodium methoxide (54 mg, 1 mmol) was added. After the solution was stirred for 2.5 h at rt, the solvent was evaporated under reduced pressure. The product was chromatographed on silica gel with dichloromethane : hexane (2:1) mixture then dichloromethane : acetone : methanol (100:40:8) mixture as eluent. **3a** and **7** were isolated in 34 and 71 % yields, respectively.

Methyl 2-methoxycarbonylbenzenesulfenate (7).

^{1}H NMR ($CDCl_3$) δ 3.79 (3H, s), 3.93 (3H, s), 7.17-7.22 (1H, m), 7.61 (2H, d, J=3.6 Hz), 8.01 (1H, d, J=7.7 Hz); IR (neat) ν_{max} 1692, 1437, 1317, 1281, 988, 743, 691 cm^{-1}; HRMS Calcd for

$C_9H_{10}O_3S$: 198.0351. Found: 198.0363.

General procedure for the synthesis of 1,2-benzisothiazolin-3-ones (3) from 2-sulfenamoylbenzoates (2).

A 2-sulfenamoylbenzoate (2, 1 mmol) was dissolved in the solution of potassium hydroxide (56 mg, 1 mmol) in ethanol (20 mL). After the solution was stirred for 30 min at rt, the solvent was evaporated under reduced pressure. The product was chromatographed on *silica gel with dichloromethane : acetone : methanol* (100:40:8) mixture as eluent and further purified by recrystallization from ethanol.

1,2-Benzisothiazolin-3-one (3a).

mp 158 °C (lit.,[9] 158-159 °C); ^{1}H NMR ($CDCl_3$) δ 7.42-7.47 (1H, m), 7.65-7.67 (2H, m), 8.08 (1H, d, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 120.8, 124.2, 125.3, 125.9, 131.7, 144.8, 169.1; IR (KBr) ν_{max} 3057, 2917, 2697, 1640, 743, 608 cm^{-1}.

6-Chloro-1,2-benzisothiazolin-3-one (3c).

mp 226 °C (sublimation) (lit.,[9] 276-278 °C); ^{1}H NMR (DMSO-d_6) δ 7.46 (1H, dd, *J*=8.5, 1.6 Hz), 7.87 (1H, d, *J*=8.5 Hz), 8.18 (1H, d, *J*=1.6 Hz); IR (KBr) ν_{max} 3080, 2930, 2719, 1637, 1402, 820, 596 cm^{-1}; Anal. Calcd for C_7H_4NOClS: C, 45.29; H, 2.17; N, 7.55. Found: C, 45.22; H, 2.00; N, 7.37.

5-Chloro-1,2-benzisothiazolin-3-one (3d).

mp 180 °C (sublimation) (lit.,[9] 265-267 °C); ^{1}H NMR (DMSO-d_6) δ 7.66 (1H, dd, *J*=8.5, 2.2 Hz), 7.90 (1H, d, *J*=2.2 Hz), 8.07 (1H, d, *J*=8.5 Hz); IR (KBr) ν_{max} 3036, 2911, 2691, 1638, 1449, 1327, 1267, 1157, 1078, 621, 563 cm^{-1}; Anal. Calcd for C_7H_4NOClS: C, 45.29; H, 2.17; N, 7.55. Found: C, 45.40; H, 2.06; N, 7.41.

5,6-Dimethoxy-1,2-benzisothiazolin-3-one (3e).

mp 229-230 °C (lit.,[10] 228-229 °C); ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 3.99 (3H, s), 7.02 (1H, s), 7.44 (1H, s); IR (KBr) ν_{max} 2932, 2666, 1644, 1493, 1281, 1044 cm^{-1}.

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