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Synthesis of 1,2-benzisothiazolin-3-ones by ring transformation of 1,3-benzoxathiin-4-one 1-oxides

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ABSTRACT

1,2-Benzisothiazolin-3-ones were synthesized from 1,3-benzoxathiin-4-one 1-oxides by means of a non-hazardous and inexpensive method. The 1,3-benzoxathiin-4-one 1-oxides were prepared by oxidation of 1,3-benzoxathiin-4-ones with hydrogen peroxide in the presence of a catalyst. Attack of amines on the carbonyl groups of the 1,3-benzoxathiin-4-one 1-oxides and subsequent elimination of carbonyl compounds likely produced sulfenic acids, which then underwent ring closure to afford the 1,2-benzisothiazolin-3-ones.

1. Introduction

1,2-Benzisothiazolin-3-one and its derivatives show fungistatic, antimicrobial, and antipsychotic activities;[1] for example, 1,2-benzisothiazolin-3-one and 2-butyl-1,2-benzisothiazolin-3-one are well-known industrial biocides. Compounds with nitrogen–sulfur bonds are generally synthesized by reactions of amines with sulfenyl chlorides prepared from thiols or disulfides and chlorine gas;[2] and 1,2-benzisothiazolin-3-ones have also been synthesized by the reaction of dithiodibenzoic acids[3] or their esters[4] with chlorine gas in the same manner. Because there is a trend toward minimizing the use of hazardous reagents in synthetic chemistry, a chlorine gas-free method for the synthesis of 1,2-benzisothiazolin-3-ones is desirable. We previously reported a convenient, chlorine gas-free synthesis of 1,2-benzisothiazolin-3-ones by cyclization of 2-sulfenamoylbenzoates, which are easily prepared by *S*-amination of thiosalicylates with hydroxylamine-*O*-sulfonic acid.[5] In addition, various syntheses of 1,2-benzisothiazolin-3-one derivatives have been reported in the last decade, including reactions of thiosalicylamides with hypervalent iodine reagents[6] or *O*-methylhydroxylamine,[7] reaction of thiosalicylic acid with diphenylphospholyl azide,[8] and reactions of 2,2′-dithiodibenzoates with acetamide or urea followed by oxidation with hydrogen peroxide.[9]

Meanwhile, 1,3-benzoxathiin-4-ones can be regarded as *O*,*S*-acetals and can be easily synthesized by reactions of thiosalicylic acids with carbonyl compounds or their acetals in the presence of acids.[10,11] However, the reactivity of 1,3-benzoxathiin-4-ones has not yet been extensively studied. Reactions with nucleophiles[11,12] and oxidants[11,13,14] to afford ring-opened products and sulfoxides, respectively, have been reported. Although most of these reactions are not particularly useful for synthetic chemistry, Krische reported an interesting ring transformation of 8-carbamoyl-substituted 1,3-benzoxathiin-4-one 1-oxides to 7-carboxy-substituted 1,2-benzisothiazolin-3-ones but did not discuss the precise reaction mechanism.[13b]

Because 1,3-benzoxathiin-4-ones react with primary amines at the carbonyl groups to give ring-opened products (thiosalicylamide derivatives[12]), we expected that 1,3-benzoxathiin-4-one 1-oxides would undergo similar reactions to form the corresponding sulfenobenzamides. Sulfeno group formation is known for sulfoxides with active protons at the β-positions.[15,16] We expected the resulting 2-sulfenobenzamides to cyclize easily to 1,2-benzisothiazolin-3-ones, as reported previously.[15,17] In this paper, we report the reactions of 1,3-benzoxathiin-4-one 1-oxides with primary amines and the use of the reactions for the synthesis of 1,2-benzisothiazolin-3-ones (Scheme 1).

2. Results and discussion

First we prepared 1,3-benzoxathiin-4-one 1-oxides **2** by oxidation of 1,3-benzoxathiin-4-ones **1** with 1.5 equiv of

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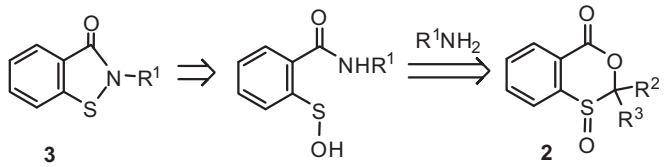
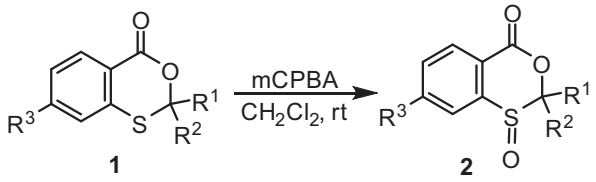


Scheme 1. Proposed strategy for the synthesis of 1,2-benzisothiazolin-3-ones **3**.

m-chloroperoxybenzoic acid (mCPBA) according to literature methods[11,13] (Table 1). Oxidation of 2-monosubstituted 1,3-benzoxathiin-4-ones afforded two products after isolation by means of silica gel column chromatography (entries 2–6); the two products were deduced to be diastereomers with referring to literature.[14] Note that although mCPBA oxidation of **1f** has been reported to afford *trans*-**2f** with high stereoselectivity,[14] we obtained **2f** as a 1.43:1 mixture of two diastereomers (entry 6).

Table 1
Oxidation of 1,3-benzoxathiin-4-ones **1** with mCPBA[a]



Entry	1	R^1	R^2	R^3	Time	Product	Yield (%)	Ratio of isomers
1	**1a**	Me	Me	H	2 h	**2a**	91	—
2	**1b**	H	H	H	2 h	**2b**	30	—
3	**1c**	Et	H	H	2 h	**2c**	80	1.27:1
4	**1d**	Et	H	MeO	3 h	**2d**	79	1.07:1
5	**1e**	*i*-Pr	H	H	40 min	**2e**	82	1.32:1
6	**1f**	Ph	H	H	2 h	**2f**	88	1.43:1

[a] Compound **1** (2 mmol); 3 mmol mCPBA; 20 mL CH_2Cl_2.

mCPBA is expensive, and oxidation reactions with mCPBA afford *m*-chlorobenzoic acid as a waste product, while hydrogen peroxide is a superior oxidation reagent because water is the only theoretical product[18] after oxidation. Therefore, oxidation with hydrogen peroxide is regarded as environmentally benign and economical.[18,19] However, it was reported that the oxidation of 1,3-benzoxathiin-4-one proceeds with mCPBA or $NaIO_4$,[13b] but the other standard oxidants[11] do not afford oxidation products. Considering these points, we next investigated the oxidation of 1,3-benzoxathiin-4-ones with hydrogen peroxide (Table 2). First, we oxidized 1,3-benzoxathiin-4-one with hydrogen peroxide in acetic acid according to the literature procedure,[13b] but none of the desired sulfoxide product was obtained even after 6 h (entry 1). However, the addition of an oxidative or acidic catalyst activated the hydrogen peroxide. For example, in the presence of sodium tungstate, **1a** was oxidized to **2a** in 72% yield after 6 h (entry 3). A heteropoly acid, such as commercially available phosphotungstic acid or phosphomolybdic acid, accelerated the oxidation, affording the sulfoxide product in a good yield after only 1 h. Interestingly, when the solvent was changed to a mixture of acetic acid and formic acid, the yield improved to 90% even in the absence of a catalyst (entry 2). Methyltrioxorhenium(VII) also effectively catalyzed the oxidation, and the sulfoxides were obtained in excellent yields (entries 6–8). In summary, the use of an oxidative catalyst or formic acid as a solvent allowed us to oxidize 1,3-benzoxathiin-4-ones rapidly in good yields.

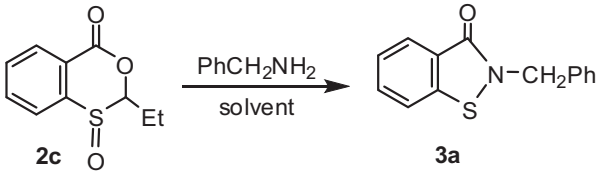
Table 2
Oxidation of 1,3-benzoxathiin-4-ones **1** with hydrogen peroxide[a]

Entry	1	Catalyst (mol %)	Solvent	Time (h)	Product	Yield (%)
1	**1a**	—	AcOH	6	—	—
2	**1a**	—	AcOH, HCO_2H[b]	1	**2a**	90
3	**1a**	Na_2WO_4 (1)	AcOH	6	**2a**	72
4	**1a**	$H_3PW_{12}O_{40}\cdot nH_2O$ (2)	AcOH	1	**2a**	79
5	**1a**	$H_3PMo_{12}O_{40}\cdot nH_2O$ (4)	AcOH	1	**2a**	82
6	**1a**	$MeReO_3$ (4)	CH_2Cl_2	4	**2a**	97
7	**1c**	$MeReO_3$ (4)	CH_2Cl_2	1	**2c**	78
8	**1f**	$MeReO_3$ (4)	CH_2Cl_2	0.5	**2f**	91

[a] Compound **1** (1 mmol); 1.5 mmol 30% H_2O_2; 20 mL solvent; rt.
[b] 1:1 mixture.

Next, we investigated the reactions of 1,3-benzoxathiin-4-one 1-oxides **2** with primary amines in various solvents (Table 3). (Note that the reactions were carried out on the mixtures of the 2-monosubstituted 1,3-benzoxathiin-4-one 1-oxide diastereomers.) When **2c** was treated with benzylamine in toluene for 2 h at 50 °C, 2-benzyl-1,2-benzisothiazolin-3-one (**3a**) was isolated in 91% yield; the identity of the product was confirmed by comparison of its spectral data with spectral data[20] for **3a** prepared by a literature method. No reaction intermediates were observed. The ring transformations also proceeded in good yields in all the other solvents, except alcohols. Reaction of the 1,3-benzoxathiin-4-one 1-oxides with various amines in toluene afforded the desired 1,2-benzisothiazolin-3-ones (Table 4). No steric effects were observed in the reactions between benzylamine and the 2-substituted benzoxathiin-4-ones (entries 1–3, 17, 18). However, the yields of reaction with anilines or sterically hindered amines were low, and high reaction temperatures were required to improve the yields of **3**.

Table 3
Effect of solvent on the synthesis of 1,2-benzisothiazolin-3-one **3a**[a]

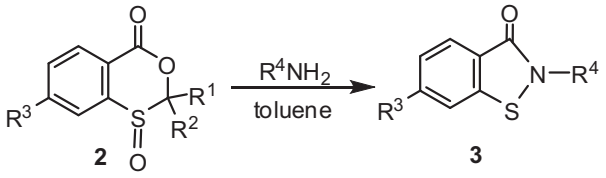


Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Toluene	50	2	91
2	CH_2Cl_2	Reflux	4	89
3	MeCN	50	2.5	80
4	Cyclopentyl methyl ether	50	3	90
5	THF	50	2	96
6	MeOH	50	0.5	5
7	EtOH	50	1.5	43

[a] Compound **2c** (1 mmol); 3 mmol benzylamine; 10 mL solvent.

We propose the reaction mechanism outlined in Scheme 2 for the formation of compounds **3**. 1,3-Benzoxathiin-4-ones **1** can be regarded as *O*,*S*-acetals formed by reaction of carbonyl compounds with thiosalicylic acid. In the same manner, 1,3-benzoxathiin-4-one 1-oxides can be regarded as *O*,*S*-acetals formed by reaction of carbonyl compounds with 2-hydrosulfinobenzoic acid, which is a tautomer of 2-sulfenobenzoic acid.[21] Attack of an amine on the carbonyl group of a 1,3-benzoxathiin-4-one resulted in elimination of the carbonyl compound and production of a thiol compound.[11,12b] We propose that similar ring-opening reactions of 1,3-benzoxathiin-4-one 1-oxides resulted in the formation of 2-carbonylbenzenesulfenic acids by elimination of carbonyl compounds. An eliminated carbonyl compound, benzaldehyde, was in fact isolated in 63% yield from the reaction of **2f** with butylamine. The amide nitrogen atoms of the intermediates attacked the sulfur atoms, and subsequent dehydration resulted in the formation of the 1,2-benzisothiazolin-3-one. Note that the formation of 2-sulfenobenzamide intermediates and subsequent formation of 1,2-benzisothiazolin-3-one have been reported previously,[15,17] and these previous reports support our proposed reaction mechanism.

Table 4
Synthesis of 1,2-benzisothiazolin-3-ones **3**[a]



Entry	2	R^1	R^2	R^3	R^4	Temp (°C)	Time (h)	Product	Yield (%)
1	**2a**	Me	Me	H	$PhCH_2$	50	6	**3a**	84
2	**2b**	H	H	H	$PhCH_2$	50	5	**3a**	92
3	**2c**	Et	H	H	$PhCH_2$	50	2	**3a**	91
4	**2c**	Et	H	H	$PhCH_2CH_2$	50	2	**3b**	84
5	**2c**	Et	H	H	Bu	50	3	**3c**	89
6	**2c**	Et	H	H	$HO(CH_2)_2$	50	3	**3d**	68
7	**2c**	Et	H	H	$HO(CH_2)_3$	50	2	**3e**	83
8	**2c**	Et	H	H	Cyclohexyl	Reflux	2	**3f**	70
9	**2c**	Et	H	H	*p*-$MeOC_6H_4$	Reflux	4	**3g**	74
10	**2c**	Et	H	H	*p*-MeC_6H_4	Reflux	6	**3h**	76
11	**2c**	Et	H	H	Ph	Reflux	7	**3i**	75
12	**2c**	Et	H	H	*p*-ClC_6H_4	Reflux	8	**3j**	75
13	**2c**	Et	H	H	Me_3C	110[b]	7	**3k**	59
14	**2c**	Et	H	H	2-Pyridyl	Reflux	6	**3l**	45
15	**2c**	Et	H	H	H[c]	50[b]	6	**3m**	43
16	**2d**	Et	H	MeO	$PhCH_2$	50	3	**3n**	100
17	**2e**	*i*-Pr	H	H	$PhCH_2$	50	6	**3a**	82
18	**2f**	Ph	H	H	$PhCH_2$	50	3	**3a**	93
19	**2f**	Ph	H	H	Bu	50	3	**3c**	84

[a] Compound **2** (1 mmol); 3 mmol amine; 10 mL solvent.
[b] In a sealed tube.
[c] As a 1,4-dioxane solution.

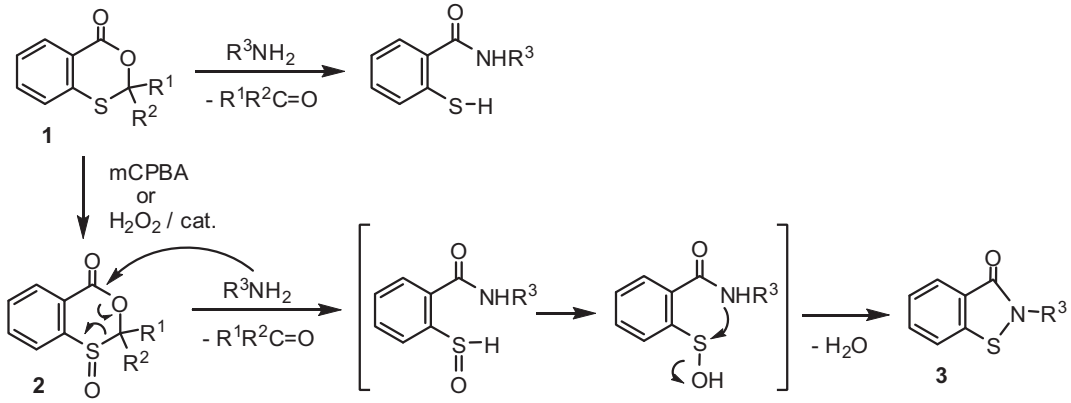
Chromatographic separation of products was performed on silica gel 60 (Merck, 70–230 mesh). Thin layer chromatography was performed on plates precoated with silica gel 60 (Merck). 1,3-Benzoxathiin-4-ones **1** were prepared according to literature procedures.[10a,11]

*3.1.1. 2,2-Dimethylbenzo[d]-1,3-oxathiin-4-one (**1a**).*[11] Bp 157 °C (1.1×10^2 Pa); ν_{max} (liquid film) 1724, 1593, 1441, 1287, 1247, 1172, 1093, 1051, 960, 744 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.84 (6H, s), 7.28 (1H, d, *J* 7.3 Hz), 7.29 (1H, d, *J* 7.3 Hz), 7.49 (1H, d, *J* 7.3 Hz), 8.18 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 29.1, 86.2, 123.5, 126.3, 127.9, 132.1, 133.9, 136.9, 163.5.

*3.1.2. Benzo[d]-1,3-oxathiin-4-one (**1b**).*[11] Bp 175 °C (1.3×10^2 Pa); δ_H (500 MHz, $CDCl_3$) 5.43 (2H, s), 7.34 (2H, t, *J* 7.3 Hz), 7.36 (1H, d, *J* 7.3 Hz), 7.49 (1H, t, *J* 7.3 Hz), 8.19 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 68.8, 124.5, 126.9, 127.7, 132.8, 133.5, 138.8, 163.3.

*3.1.3. 2-Ethylbenzo[d]-1,3-oxathiin-4-one (**1c**).* Bp 173 °C (1.7×10^2 Pa); [Found: C, 62.25; H, 5.14. $C_{10}H_{10}O_2S$ requires C, 61.83; H, 5.19%]; ν_{max} (liquid film) 2973, 1729, 1593, 1461, 1442, 1296, 1275, 1247, 1224, 1125, 1095, 1051, 1032, 973, 942 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.6 Hz), 2.04–2.21 (2H, m), 5.54 (1H, t, *J* 6.1 Hz), 7.29–7.34 (2H, m), 7.48 (1H, ddd, *J* 7.9, 7.3, 1.5 Hz), 8.17 (1H, dd, *J* 7.9, 1.2 Hz); δ_C (125 MHz, $CDCl_3$) 9.6, 27.7, 84.3, 124.3, 126.6, 127.7, 132.6, 133.5, 138.5, 164.3.

*3.1.4. 2-Ethyl-7-methoxybenzo[d]-1,3-oxathiin-4-one (**1d**).* Bp 235 °C (1.1×10^2 Pa); [Found: C, 58.97; H, 5.17. $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39%]: ν_{max} (liquid film) 2973, 1720, 1596, 1488, 1256, 1089, 1043, 975, 768 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.15 (3H, t, *J* 7.3 Hz), 2.03–2.19 (2H, m), 3.86 (3H, s), 5.54 (1H, t, *J* 6.1 Hz), 6.79 (1H, d, *J* 2.4 Hz), 6.82 (1H, dd, *J* 8.5, 2.4 Hz), 8.12 (1H, d, *J* 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 9.5, 27.7, 55.7, 89.9, 111.7, 113.4, 116.6, 134.6, 140.7, 163.4, 164.3.



Scheme 2. Mechanism of formation of 1,2-benzisothiazolin-3-ones **3** from 1,3-benzoxathiin-4-ones **1**.

In summary, we prepared 1,2-benzisothiazolin-3-ones in good yields by means of reactions of amines with 1,3-benzoxathiin-4-one 1-oxides formed by oxidation of 1,3-benzoxathiin-4-ones with hydrogen peroxide. Thus, 1,2-benzisothiazolin-3-ones were synthesized by means of a convenient and environmentally benign method.

3. Experimental section

3.1. General

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a JEOL LA-500 spectrometer, and chemical shifts are given relative to internal tetramethylsilane (^1H NMR) or $CDCl_3$ (^{13}C NMR). IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer.

*3.1.5. 2-Isopropylbenzo[d]-1,3-oxathiin-4-one (**1e**).*[10a,22] Bp 171 °C (1.8×10^2 Pa); ν_{max} (liquid film) 2966, 1729, 1442, 1279, 1099, 1033, 741 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.17 (3H, d, *J* 7.3 Hz), 1.18 (3H, d, *J* 7.3 Hz), 2.34 (1H, d–septet, *J* 7.3, 6.1 Hz), 5.43 (1H, d, *J* 6.1 Hz), 7.30 (1H, t, *J* 7.3 Hz), 7.35 (1H, d, *J* 7.3 Hz), 7.47 (1H, t, *J* 7.3 Hz), 8.17 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 18.2, 18.4, 32.6, 88.7, 124.3, 126.4, 127.9, 132.5, 133.4, 138.6, 164.4.

*3.1.6. 2-Phenylbenzo[d]-1,3-oxathiin-4-one (**1f**).* Mp 90.7–91.6 °C (hexane) [lit.[23] 90 °C]; δ_H (500 MHz, $CDCl_3$) 6.57 (1H, s), 7.34–7.38

(2H, m), 7.43–7.45 (3H, m), 7.52 (1H, td, *J* 7.9, 1.5 Hz), 7.60 (2H, dd, *J* 7.9, 2.1 Hz), 8.23 (1H, ddd, *J* 7.9, 1.5, 0.6 Hz); δ_C (125 MHz, $CDCl_3$) 83.7, 124.3, 126.8, 126.9, 127.4, 128.8, 129.9, 132.8, 133.8, 134.7, 138.7, 164.0.

3.2. General procedure for the synthesis of 1,3-benzoxathiin-4-one 1-oxides 2 with mCPBA

1,3-Benzoxathiin-4-one (**1**, 2.0 mmol) was dissolved in dichloromethane (20 mL), and mCPBA (518 mg, 3.0 mmol) was added. The solution was stirred at room temperature for 40 min to 3 h. Then saturated aqueous sodium sulfite was added until no peroxide compound was observed with peroxide test paper, and products were extracted with dichloromethane. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent with a rotary evaporator afforded the crude product, which was purified by chromatography on silica gel with an appropriate eluent.

*3.2.1. 2,2-Dimethylbenzo[d]-1,3-oxathiin-4-one 1-oxide (**2a**).*[11] R_f (CH_2Cl_2/AcOEt=10:1) 0.4; δ_H (500 MHz, $CDCl_3$) 1.70 (3H, s), 1.74 (3H, s), 7.72 (1H, td, *J* 7.5, 1.8 Hz), 7.82–7.89 (2H, m), 8.22 (1H, dd, *J* 7.5, 0.9 Hz); δ_C (125 MHz, $CDCl_3$) 20.5, 24.6, 94.0, 122.3, 128.6, 131.8, 132.5, 135.2, 140.7, 160.5.

*3.2.2. Benzo[d]-1,3-oxathiin-4-one 1-oxide (**2b**).*[13a] R_f (CH_2Cl_2/acetone/MeOH=100:10:2) 0.4; δ_H (500 MHz, $CDCl_3$) 5.31 (1H, d, *J* 11.0 Hz), 5.41 (1H, d, *J* 11.0 Hz), 7.79 (1H, td, *J* 7.3, 2.4 Hz), 7.87 (2H, q, *J* 7.3 Hz), 8.29 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 80.3, 122.1, 128.0, 132.6, 133.3, 135.1, 142.1, 160.6.

*3.2.3. 2-Ethylbenzo[d]-1,3-oxathiin-4-one 1-oxide (**2c**).* (Isomer 1): mp 79.7–80.4 °C (AcOEt/hexane); [Found: C, 57.18; H, 4.71. $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.4; δ_H (500 MHz $CDCl_3$) 1.27 (3H, t, *J* 7.3 Hz), 2.23 (1H, septet, *J* 7.3 Hz), 2.36 (1H, dqd, *J* 14.6, 7.3, 3.7 Hz), 5.11 (1H, dd, *J* 7.3, 3.7 Hz), 7.69 (1H, t, *J* 7.3 Hz), 7.86 (1H, t, *J* 7.3 Hz), 7.92 (1H, d, *J* 7.3 Hz), 8.15 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 8.7, 23.1, 95.4, 121.3, 125.5, 131.5, 132.1, 135.3, 145.5, 161.4.

(Isomer 2): mp 87.1–88.1 °C (AcOEt/hexane); [Found: C, 57.28; H, 4.63. $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.25; δ_H (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.3 Hz), 2.31 (2H, quintet, *J* 7.3 Hz), 4.99 (1H, t, *J* 7.3 Hz), 7.81–7.88 (3H, m), 8.36 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 8.9, 23.4, 91.5, 122.9, 130.1, 132.6, 134.1, 134.8, 139.6, 161.5.

*3.2.4. 2-Ethyl-7-methoxybenzo[d]-1,3-oxathiin-4-one 1-oxide (**2d**).* (Isomer 1): mp 123.3–124.1 °C (AcOEt/hexane); [Found: C, 55.01; H, 4.93. $C_{11}H_{12}O_4S$ requires C, 54.99; H, 5.03%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.5; δ_H (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.3 Hz), 2.23 (1H, ddq, *J* 14.6, 8.5, 7.3 Hz), 2.37 (1H, dqd, *J* 14.6, 7.3, 3.7 Hz), 3.97 (3H, s), 5.09 (1H, dd, *J* 7.3, 3.7 Hz), 7.10 (1H, dd, *J* 8.5, 2.4 Hz), 7.36 (1H, d, *J* 2.4 Hz), 8.07 (1H, d, *J* 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 8.6, 23.1, 56.2, 95.2, 109.6, 113.0, 117.8, 134.4, 148.0, 161.4, 165.1.

(Isomer 2): mp 111.5–112.2 °C (AcOEt/hexane); [Found: C, 55.06; H, 4.94. $C_{11}H_{12}O_4S$ requires C, 54.99; H, 5.03%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.3; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.3 Hz), 2.28 (2H, ddq, *J* 14.6, 9.7, 7.3 Hz), 3.97 (3H, s), 4.98 (1H, t, *J* 7.3 Hz), 7.23 (1H, dd, *J* 8.5, 2.4 Hz), 7.32 (1H, d, *J* 2.4 Hz), 8.28 (1H, d, *J* 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 8.9, 23.2, 56.2, 91.3, 114.7, 115.0, 119.2, 134.8, 141.5, 161.4, 164.3.

*3.2.5. 2-Isopropylbenzo[d]-1,3-oxathiin-4-one 1-oxide (**2e**).* (Isomer 1): mp 79.3–80.5 °C (AcOEt/hexane); [Found: C, 58.84; H, 5.37. $C_{11}H_{12}O_3S$ requires C, 58.91; H, 5.39%]; R_f (CH_2Cl_2/AcOEt=20:1) 0.5; ν_{max} (KBr) 2968, 1750, 1590, 1464, 1444, 1271, 1246, 1227, 1053, 1029, 1008, 975, 746, 698, 680, 532 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.3 Hz), 1.31 (3H, d, *J* 7.3 Hz), 2.66 (1H, septet–doublet, *J* 7.3, 2.4 Hz), 5.04 (1H, d, *J* 2.4 Hz), 7.68 (1H, t, *J* 7.3 Hz), 7.86 (1H, t, *J* 7.3 Hz), 7.93 (1H, d, *J* 7.3 Hz), 8.14 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 15.8, 18.3, 28.0, 98.7, 121.2, 125.4, 131.3, 132.0, 135.2, 145.6, 161.5.

(Isomer 2): mp 139.3–140.4 °C (AcOEt/hexane); [Found: C, 58.95; H, 5.37. $C_{11}H_{12}O_3S$ requires C, 58.91; H, 5.39%]; R_f (CH_2Cl_2/AcOEt=20:1) 0.3; ν_{max} (KBr) 2970, 1738, 1297, 1267, 1242, 1092, 1053, 1029, 751, 687, 527 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.3 Hz), 1.33 (3H, d, *J* 7.3 Hz), 2.65 (1H, doublet–septet, *J* 8.5, 7.3 Hz), 4.65 (1H, d, *J* 8.5 Hz), 7.80–7.87 (3H, m), 8.35 (1H, t, *J* 4.9 Hz); δ_C (125 MHz, $CDCl_3$) 17.9, 18.4, 29.2, 95.4, 123.0, 130.0, 134.2, 134.7, 139.6, 161.8.

*3.2.6. 2-Phenylbenzo[d]-1,3-oxathiin-4-one 1-oxide (**2f**).*[13a,14] (Isomer 1): mp 129.9–131.8 °C (AcOEt/hexane) [lit.[13a] 142 °C, lit.[14] 130–132 °C]; [Found: C, 65.06; H, 3.75. $C_{14}H_{10}O_3S$ requires C, 65.10; H, 3.90%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.5; ν_{max} (KBr) 1730, 1589, 1444, 1273, 1246, 1100, 1063, 1014, 746, 700 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.03 (1H, s), 7.50–7.52 (3H, m), 7.62–7.64 (2H, m), 7.73 (1H, t, *J* 7.3 Hz), 7.90 (1H, t, *J* 7.3 Hz), 7.96 (1H, d, *J* 7.3 Hz), 8.21 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 95.6, 121.4, 125.7, 127.6, 129.1, 130.3, 130.9, 131.7, 132.3, 135.5, 145.6, 161.4.

(Isomer 2): mp 143.2–144.2 °C (AcOEt/hexane) [lit.[13a] 146 °C, lit.[14] 134–135 °C]; [Found: C, 65.24; H, 3.71. $C_{14}H_{10}O_3S$ requires C, 65.10; H, 3.90%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.4; ν_{max} (KBr) 1746, 1589, 1496, 1449, 1279, 1248, 1102, 1050, 792, 774, 751, 699, 526, 475, 427 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.15 (1H, s), 7.47–7.54 (3H, m), 7.63–7.65 (2H, m), 7.84–7.90 (3H, m), 8.40–8.43 (1H, m); δ_C (125 MHz, $CDCl_3$) 91.0, 122.8, 127.2, 129.2, 130.5, 131.2, 132.8, 134.2, 134.9, 140.5, 161.9.

3.3. General procedure for the synthesis of 1,3-benzoxathiin-4-one 1-oxides (2) with hydrogen peroxide

To a solution (20 mL) of 1,3-benzoxathiin-4-one (**1**, 1.0 mmol) and catalyst in appropriate solvent, 30% aqueous hydrogen peroxide (1.5 mmol) was added dropwise. The solution was stirred at room temperature for 0.5–6 h. Then saturated sodium sulfite aqueous solution was added until no peroxide compound was observed with peroxide test paper, and the products were extracted with dichloromethane. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent afforded the crude product, which was purified by chromatography on silica gel with an appropriate eluent.

3.4. General procedure for the synthesis of 1,2-benzisothazolin-3-ones (3)

1,3-Benzoxathiin-4-one 1-oxide (**2**, 1.0 mmol) and the appropriate amine or aniline (3 mmol) were stirred in toluene (10 mL) at 50–100 °C until **2** was consumed (2–8 h). After the solvent was removed by evaporation, the products were purified by silica gel chromatography with an appropriate eluent. In the case of **3m**, a 1,4-dioxane solution of ammonia (0.5 M) was used.

*3.4.1. 2-Benzyl-1,2-benzisothiazolin-3-one (**3a**).* Mp 87.0–87.7 °C (AcOEt/hexane) [lit.[20] 85.5–87 °C (*i*-PrOH)]; R_f (CH_2Cl_2/AcOEt=20:1) 0.4; δ_H (500 MHz, $CDCl_3$) 5.06 (2H, s), 7.31–7.36 (5H, m), 7.41 (1H, t, *J* 7.3 Hz), 7.49 (1H, d, *J* 7.3 Hz), 7.59 (1H, t, *J* 7.3 Hz), 8.07 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 47.5, 120.4, 124.5, 125.5, 126.8, 128.3, 128.4, 128.8, 131.8, 136.2, 140.4, 165.3.

*3.4.2. 2-(2-Phenylethyl)-1,2-benzisothiazolin-3-one (**3b**).* Mp 92.8–93.4 °C (hexane) [lit.[24] 92.5–93.5 °C (hexane)]; R_f (CH_2Cl_2/AcOEt=10:1) 0.67; δ_H (500 MHz, $CDCl_3$) 3.07 (2H, t, *J* 7.3 Hz), 4.13

(2H, t, *J* 7.3 Hz), 7.22–7.26 (3H, m), 7.30 (2H, t, *J* 7.3 Hz), 7.39 (1H, t, *J* 7.3 Hz), 7.51 (1H, d, *J* 7.3 Hz), 7.59 (1H, t, *J* 7.3 Hz), 8.03 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 35.6, 45.4, 120.3, 124.6, 125.4, 126.6, 126.8, 128.7, 128.9, 131.7, 137.7, 140.2, 165.3.

*3.4.3. 2-Butyl-1,2-benzoisothiazoline-3-one (**3c**).*[7] Bp 180 °C (1.1×10^2 Pa); R_f (CH_2Cl_2/AcOEt=20:1) 0.4; δ_H (500 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.3 Hz), 1.42 (2H, sextet, *J* 7.3 Hz), 1.75 (2H, quintet, *J* 7.3 Hz), 3.90 (2H, t, *J* 7.3 Hz), 7.40 (1H, t, *J* 7.3 Hz), 7.55 (1H, d, *J* 8.5 Hz), 7.60 (1H, t, *J* 7.3 Hz), 8.04 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 13.7, 19.8, 31.6, 43.7, 120.3, 124.9, 125.4, 126.7, 131.6, 140.1, 165.3.

*3.4.4. 2-(2-Hydroxyethyl)-1,2-benzisothiazolin-3-one (**3d**).* Mp 110.6–112.0 °C (AcOEt/hexane) [lit.[4] 112–114 °C (acetone)]; R_f (CH_2Cl_2/acetone/MeOH=100:40:8) 0.4; δ_H (500 MHz, $CDCl_3$) 3.48 (1H, br s), 3.95 (2H, q, *J* 4.9 Hz), 4.03 (2H, t, *J* 4.9 Hz), 7.38 (1H, t, *J* 7.3 Hz), 7.53 (1H, d, *J* 7.3 Hz), 7.60 (1H, t, *J* 7.3 Hz), 8.00 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 47.5, 62.0, 120.2, 124.2, 125.6, 126.6, 131.9, 140.7, 166.4.

*3.4.5. 2-(3-Hydroxypropyl)-1,2-benzisothiazolin-3-one (**3e**).* Mp 75.3–76.6 °C (AcOEt/hexane) [lit.[20] 76.6–77.4 °C (AcOEt)]; R_f (CH_2Cl_2/acetone/MeOH=100:40:8) 0.5; δ_H (500 MHz, $CDCl_3$) 1.92 (2H, quintet, *J* 6.1 Hz), 3.57 (2H, q, *J* 6.1 Hz), 3.62–3.65 (1H, m), 4.08 (2H, t, *J* 6.1 Hz), 7.44 (1H, t, *J* 7.3 Hz), 7.58 (1H, d, *J* 7.3 Hz), 7.64 (1H, d, *J* 7.3 Hz), 8.05 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 31.9, 40.4, 57.8, 120.4, 124.1, 125.7, 126.8, 132.0, 140.3, 166.4.

*3.4.6. 2-Cyclohexyl-1,2-benzisothiazolin-3-one (**3f**).* Mp 87.2–88.0 °C (hexane) [lit.[4] 86–88 °C (diethylether/hexane)]; R_f (CH_2Cl_2/AcOEt=20:1) 0.4; δ_H (500 MHz, $CDCl_3$) 1.17–1.27 (1H, m), 1.43–1.60 (4H, m), 1.74 (1H, d, *J* 12.2 Hz), 1.85–1.90 (2H, m), 2.05 (2H, dd, *J* 11.6, 3.7 Hz), 4.60 (1H, tt, *J* 11.6, 3.7 Hz), 7.39 (1H, t, *J* 7.3 Hz), 7.55–7.60 (2H, m), 8.04 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 25.2, 25.6, 32.9, 53.2, 120.3, 125.3, 125.5, 126.5, 131.4, 140.3, 164.8.

*3.4.7. 2-(p-Methoxyphenyl)-1,2-benzisothiazolin-3-one (**3g**).* Mp 146.2–147.5 °C (AcOEt/hexane) [lit.[4] 147–149 °C (EtOH)]; R_f (CH_2Cl_2/hexane=2:1 on alumina) 0.33; δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s), 6.99 (2H, dd, *J* 7.3, 2.4 Hz), 7.45 (1H, t, *J* 7.3 Hz), 7.54–7.56 (2H, m), 7.58 (1H, d, *J* 7.3 Hz), 7.66 (1H, t, *J* 7.3 Hz), 8.10 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 55.6, 114.6, 120.1, 124.6, 125.7, 126.9, 127.2, 129.7, 132.2, 140.0, 158.7, 164.3.

*3.4.8. 2-(p-Methylphenyl)-1,2-benzisothiazolin-3-one (**3h**).* Mp 136.1–136.7 °C (AcOEt/hexane) [lit.[20] 136.7–137.1 °C (benzene/hexane)]; R_f (CH_2Cl_2/AcOEt=20:1) 0.5; δ_H (500 MHz, $CDCl_3$) 2.40 (3H, s), 7.27 (2H, d, *J* 8.2 Hz), 7.44 (1H, ddd, *J* 8.2, 6.9, 0.9 Hz), 7.55–7.59 (3H, m), 7.66 (1H, ddd, *J* 8.2, 6.9, 0.9 Hz), 8.10 (1H, dt, *J* 8.2, 0.9 Hz).

*3.4.9. 2-Phenyl-1,2-benzisothiazolin-3-one (**3i**).* Mp 138.5–140.3 °C (AcOEt/hexane) [lit.[20] 138–140 °C (EtOH)]; R_f (CH_2Cl_2/AcOEt=20:1) 0.5; δ_H (500 MHz, $CDCl_3$) 7.33 (1H, t, *J* 7.3 Hz), 7.44–7.49 (3H, m), 7.59 (1H, d, *J* 7.3 Hz), 7.67 (1H, t, *J* 7.3 Hz), 7.71 (2H, d, *J* 7.3 Hz), 8.11 (1H, d, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$) 120.1, 124.6, 124.8, 125.8, 127.0, 127.2, 129.3, 132.3, 137.2, 139.9, 164.1.

*3.4.10. 2-(p-Chlorophenyl)-1,2-benzisothiazolin-3-one (**3j**).* Mp 122.6–124.0 °C (AcOEt) [lit.[4] 129–130 °C (EtOH)]; R_f (CH_2Cl_2) 0.4; δ_H (500 MHz, $CDCl_3$) 7.43–7.49 (3H, m), 7.59 (1H, d, *J* 8.5 Hz), 7.67 (3H, d, *J* 8.5 Hz), 8.10 (1H, d, *J* 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 120.1, 124.6, 125.6, 126.0, 127.3, 129.5, 132.5, 132.6, 135.8, 139.6, 164.1.

*3.4.11. 2-tert-Butyl-1,2-benzisothiazolin-3-one (**3k**).*[24] Bp 150 °C (1.8×10^2 Pa); R_f (CH_2Cl_2/acetone/MeOH=100:5:1) 0.6; δ_H (500 MHz, $CDCl_3$) 1.71 (9H, s), 7.36 (1H, t, *J* 7.3 Hz), 7.50 (1H, d, *J* 8.5 Hz), 7.57 (1H, t, *J* 7.3 Hz), 7.96 (1H, d, *J* 8.5 Hz).

*3.4.12. 2-(2-Pyridyl)-1,2-benzisothiazolin-3-one (**3l**).* Mp 197.4–197.9 °C (AcOEt/hexane) [lit.[25] 194.5–195.5 °C ($CHCl_3$)]; R_f (CH_2Cl_2/AcOEt=20:1) 0.67; δ_H (500 MHz, $CDCl_3$) 7.15 (1H, ddd, *J* 7.3, 4.9, 0.9 Hz), 7.41 (1H, ddd, *J* 7.9, 7.0, 0.9 Hz), 7.59 (1H, dt, *J* 7.9, 0.9 Hz), 7.66 (1H, ddd, *J* 7.9, 7.3, 1.2 Hz), 7.81 (1H, ddd, *J* 8.2, 7.3, 1.8 Hz), 8.07 (1H, dt, *J* 7.9, 0.9 Hz), 8.42 (1H, ddd, *J* 4.9, 1.8, 0.9 Hz), 8.75 (1H, dt, *J* 8.2, 0.9 Hz); δ_C (125 MHz, $CDCl_3$) 114.5, 120.3, 120.7, 125.5, 126.6, 126.8, 132.8, 138.4, 141.0, 147.6, 150.4, 164.0.

*3.4.13. 1,2-Benzisothiazolin-3-one (**3m**).* Mp 153.3–155.9 °C (AcOEt/hexane) [lit.[5] 158 °C (EtOH)]; R_f (CH_2Cl_2/acetone/MeOH=100:10:2) 0.3; δ_H (500 MHz, $CDCl_3$) 7.45 (1H, ddd, *J* 7.8, 5.0, 3.2 Hz), 7.65–7.66 (2H, m), 8.08 (1H, dt, *J* 7.8, 1.0 Hz).

*3.4.14. 2-Benzyl-6-methoxy-1,2-benzisothiazolin-3-one (**3n**).* Mp 114.4–115.0 °C (AcOEt/hexane); [Found: C, 65.22; H, 4.64; N, 5.00. $C_{15}H_{13}NO_2S$ requires C, 66.40; H, 4.83; N, 5.16%]; R_f (CH_2Cl_2/AcOEt=10:1) 0.4; δ_H (500 MHz, $CDCl_3$) 3.86 (3H, s), 5.02 (2H, s), 6.90 (1H, d, *J* 2.1 Hz), 6.96 (1H, dd, *J* 8.7, 2.1 Hz), 7.30–7.37 (5H, m), 7.95 (1H, d, *J* 8.7 Hz); δ_C (125 MHz, $CDCl_3$) 47.5, 55.8, 103.1, 114.6, 117.7, 127.9, 128.2, 128.4, 128.8, 136.4, 142.6, 162.9, 165.2.

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