

A Practical Synthesis of N-Substituted 1,2-Benzisothiazolin-3-ones from N,N'-Disubstituted 2,2'-Dithiodibenzamides

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Abstract: A variety of N-substituted 1,2-benzisothiazolin-3-ones were easily synthesized from N,N'-disubstituted 2,2'-dithiodibenzamides in the presence of *O*-methylhydroxylamine hydrochloride. Derivatives with a primary, secondary, or tertiary alkyl group or an aryl group on the N-1 nitrogen of the 1,2-benzisothiazolin-3-one were obtained.

Key words: benzisothiazoles, disulfides, amides, hydroxylamines, oximes

The synthesis of 1,2-benzisothiazolin-3-ones and their derivatives is of widespread interest owing to their effective antifungal, antibacterial, and antipsychotic properties.¹ In general, 1,2-benzisothiazolin-3-ones are synthesized by reacting the appropriate amines with arylsulfonyl chlorides that have been previously prepared by reacting dithiosalicylic acids or their esters with chlorine gas.^{1a} However, chlorine is hazardous and poisonous, and its use in the laboratory is sometimes restricted to prevent accidents. Thus, the chlorine gas-free synthesis of 1,2-benzisothiazolin-3-ones has emerged.² Recently, we demonstrated that 1,2-benzisothiazolin-3-ones can be conveniently synthesized by S-amination of thiosalicylates with hydroxylamine-*O*-sulfonic acid (HOSA) followed by treatment with base.³ N,N'-Disubstituted 2,2'-dithiodibenzamides have also been used as starting materials for N-substituted 1,2-benzisothiazolin-3-ones. When the 2,2'-dithiodibenzamides were treated with bromine,^{4,5} iodide,⁶ or *N*-bromosuccinimide (NBS),⁷ the corresponding 1,2-benzisothiazolin-3-ones were obtained. 1,2-Benzisothiazolin-3-ones were also prepared from 2,2'-dithiodibenzamides in the presence of base or acid,⁴ but the yields were low because the produced 2-mercaptobenzamides was unavoidably oxidized to 2,2'-dithiodibenzamides by atmospheric oxygen.⁸ While we were attempting to develop a new method for the synthesis of 1,2-benzisothiazolin-3-ones, we found that the reaction of 2,2'-dithiodibenzamides with *O*-methylhydroxylamine gave 1,2-benzisothiazolin-3-ones in good yield. It was reported that *O*-alkylhydroxylamines behaved as an aminating agent.⁹ In this paper, we report that various N-substituted 1,2-benzisothiazolin-3-ones can be synthe-

sized by reacting N,N'-disubstituted 2,2'-dithiodibenzamides with *O*-methylhydroxylamine hydrochloride.

We examined the reaction of N,N'-bis(2-phenylethyl)-2,2'-dithiodibenzamide (**1a**) with *O*-methylhydroxylamine hydrochloride (4 equiv) in the presence of pyridine (8 equiv) under reflux in propionitrile. After 3 hours, the reaction mixture was purified to give 2-(2-phenylethyl)-1,2-benzisothiazolin-3-one (**2a**) in 95% yield¹⁰ (Table 1, entry 1). When acetonitrile was used as a solvent, the yield of **2a** lowered to 79% (entry 2). The reaction was carried out for various N,N'-disubstituted 2,2'-dithiodibenzamides **1** and the results are summarized in Table 1. When the N-substituent of amide **1** was a primary alkyl (entries 1, 3, and 4) or secondary alkyl (entries 5 and 6), the corresponding N-substituted 1,2-benzisothiazolin-3-ones **2** were obtained in excellent yields; good yields were obtained in the case of a tertiary alkyl (entries 7 and 8). *N*-Arylamides gave moderate yields of *N*-arylbenzisothiazolin-

Table 1 Synthesis of N-Substituted 1,2-Benzisothiazolin-3-ones **2**^a

Entry	1	R	2	Yield (%)
1	1a	PhCH ₂ CH ₂	2a	95
2 ^b	1a	PhCH ₂ CH ₂	2a	79
3	1b	Bu	2b	97
4	1c	HOCH ₂ CH ₂ CH ₂	2c	91
5	1d	<i>i</i> -Pr	2d	87
6	1e	<i>c</i> -C ₃ H ₇	2e	93
7	1f	<i>tert</i> -Bu	2f	80
8	1g	PhMe ₂ C	2g	67
9	1h	<i>p</i> -MeC ₆ H ₄	2h	72
10 ^c	1i	<i>p</i> -MeOC ₆ H ₄	2i	63
11	1j	MeO ₂ CCH ₂	2j	63

^a 2,2'-Dithiodibenzamide: 0.5 mmol; *O*-methylhydroxylamine hydrochloride: 2 mmol; pyridine: 4 mmol; propionitrile: 5 mL.

^b In MeCN as solvent.

^c Pyridine: 12.5 mmol.

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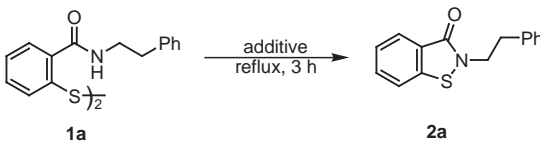
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lin-3-ones **2** (entries 9 and 10). A 1,2-benzisothiazolin-3-one **1j** derived from glycine methyl ester was also synthesized (entry 11).

Next, the effect of additives in acetonitrile was investigated, and the results are listed in Table 2. When hydroxylamine hydrochloride was used instead of *O*-methylhydroxylamine hydrochloride, the yield of **2a** was only 14% due to low solubility of the additive (entry 2). *O*-Benzylhydroxylamine hydrochloride gave **2a** in 67%, with benzyl alcohol as a by-product (entry 3). Triethylamine was an ineffective base in this reaction (entry 4). Because oximes hydrolyze to carbonyl compounds and hydroxylamines, oxime additives were also evaluated (entries 5 and 6). The oximes have good solubility in the solvent, and the yields of **2a** improved in comparison with the result of entry 2.

Table 2 Effect of Additives in the Synthesis of 2-(2-Phenylethyl)-1,2-benzisothiazolin-3-one (**2a**)^a



Entry	Additive	Yield (%)
1	MeONH ₂ ·HCl, pyridine	79
2	HONH ₂ ·HCl, pyridine	14
3	PhCH ₂ ONH ₂ ·HCl, pyridine	67 ^b
4	MeONH ₂ ·HCl, Et ₃ N	5
5	Me ₂ C=NOH	59
6 ^c	EtMeC=NOH	62

^a Entries 1–4: **1a**: 0.5 mmol; hydroxylamine hydrochloride: 2 mmol; pyridine: 4 mmol; MeCN: 5 mL. Entries 5 and 6: **1a**: 0.5 mmol; oxime: 4 mmol; solvent: 5 mL.

^b Benzyl alcohol was obtained as a by-product.

^c In propionitrile as solvent.

The mechanism for the formation of 1,2-benzisothiazolin-3-ones in these reactions is not certain. However, Ranganathan et al. reported that 2,2'-dithiodibenzamide derivatives disproportionate to 1,2-benzisothiazolin-3-ones and 2-mercaptobenzamides in the presence of acid, and that

the formed thioalicylamides are oxidized to the 2,2'-dithiodibenzamides, which, in turn, continue to disproportionate.⁸ Since *O*-methylhydroxylamine existed in the reaction mixture in our method, the sulfur atoms of the 2-mercaptobenzamides **3** were aminated to give sulfenamide derivatives **4**. As we previously reported, 2-sulfenamoylbenzamides easily cyclize to 1,2-benzisothiazolin-3-ones.¹¹ Consequently, 1,2-benzisothiazolin-3-ones **2** were obtained in good yields from 2,2'-dithiodibenzamides (Scheme 1).

In conclusion, the present synthesis of *N*-substituted 1,2-benzisothiazolin-3-ones has the following advantages: (1) good to excellent yields are obtained; (2) the synthesis can be performed with a wide variety of substrate amides (the *N*-substituent group can be a primary, secondary, or tertiary alkyl group or an aryl group); and (3) reactions are carried out under halogen-free reaction conditions.

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer. ¹H and ¹³C NMR spectra were obtained with a JEOL LA-500 spectrometer, and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane (¹H NMR) or CDCl₃ (¹³C NMR). Mass spectra were obtained with a Shimadzu QP-5000 mass spectrometer. *N,N'*-Disubstituted 2,2'-dithiodibenzamides **1** were prepared from 2,2'-dithiodibenzoyl chloride and appropriate amines.

2-(2-Phenylethyl)-1,2-benzisothiazolin-3-one (**2a**); Typical Procedure

A mixture of *N,N'*-bis(2-phenylethyl)-2,2'-dithiodibenzamide (**1a**; 255 mg, 0.5 mmol), *O*-methylhydroxylamine hydrochloride (167 mg, 2.0 mmol), and pyridine (316 mg, 4.0 mmol) in propionitrile (5 mL) was stirred for 3 h under reflux. The reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel with EtOAc–hexane (1:1) as an eluent to yield *N*-(2-phenylethyl)-1,2-benzisothiazolin-3-one (**2a**);¹¹ yield: 242 mg (95%); white crystals; mp 92.5–93.5 °C (hexane) (Lit.¹¹ mp 92.5–93.5 °C).

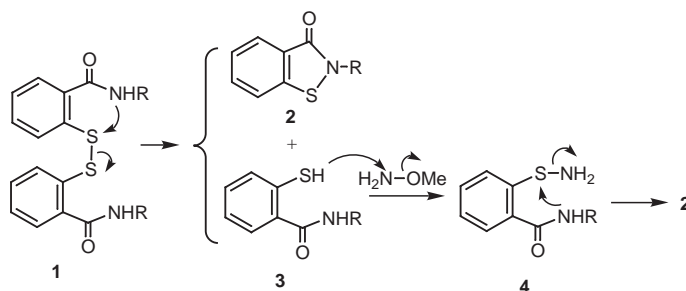
IR (KBr): 1645 (C=O), 1449, 1341, 1252, 1184, 735 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.07 (t, 2 H, *J* = 7.5 Hz), 4.13 (t, 2 H, *J* = 7.5 Hz), 7.22–7.26 (m, 3 H), 7.29–7.32 (m, 2 H), 7.39 (ddd, 1 H, *J* = 7.9, 7.6, 0.9 Hz), 7.51 (d, 1 H, *J* = 8.2 Hz), 7.59 (ddd, 1 H, *J* = 8.2, 7.6, 1.2 Hz), 8.03 (d, 1 H, *J* = 7.9 Hz).

MS: *m/z* (%) = 255 (M⁺), 164, 151 (100), 136, 108, 91.

2-Butyl-1,2-benzisothiazolin-3-one (**2b**)

Colorless oil.¹²



Scheme 1 A plausible mechanism for the formation of 1,2-benzisothiazolin-3-ones

IR (neat): 2959, 2930, 1659 (C=O), 1447, 1339, 741, 673 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 0.94 (t, 3 H, J = 7.3 Hz), 1.39 (sext, 2 H, J = 7.3 Hz), 1.73 (quint, 2 H, J = 7.3 Hz), 3.88 (t, 2 H, J = 7.3 Hz), 7.38 (ddd, 1 H, J = 7.7, 7.0, 0.9 Hz), 7.53 (dd, 1 H, J = 7.9, 0.9 Hz), 7.58 (ddd, 1 H, J = 7.9, 7.0, 1.3 Hz), 8.01 (dd, 1 H, J = 7.7, 1.3 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ = 13.6, 19.8, 31.6, 43.7, 120.3, 124.9, 235.4, 126.6, 131.6, 140.1, 165.3.

MS: m/z (%) = 207 (M^+), 190, 164, 151 (100), 136, 108.

2-(3-Hydroxypropyl)-1,2-benzisothiazoline-3-one (2c)

Chromatography on silica gel with CH_2Cl_2 -acetone-MeOH (100:20:4) mixture as eluent; white crystals; mp 76.6–77.4 °C (EtOAc) (Lit.¹³ mp 76.6–77.4 °C).

IR (KBr): 3364, 2944, 1632 (C=O), 1445, 1350, 1192, 1065, 937, 743 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.92 (tt, 2 H, J = 6.2, 5.6 Hz), 3.58 (t, 2 H, J = 5.6 Hz), 3.65 (br s, 1 H), 4.08 (t, 2 H, J = 6.2 Hz), 7.44 (ddd, 1 H, J = 8.0, 7.0, 1.1 Hz), 7.58 (dt, 1 H, J = 8.0, 1.1 Hz), 7.65 (td, 1 H, J = 7.8, 1.1 Hz), 8.05 (dt, 1 H, J = 7.8, 1.1 Hz).

MS: m/z (%) = 209 (M^+), 166, 165, 151, 136 (100), 108, 82, 69.

2-Isopropyl-1,2-benzisothiazolin-3-one (2d)

Colorless oil.¹⁴

IR (neat): 2973, 1649 (C=O), 1449, 1308, 1155, 741, 675 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.42 (d, 6 H, J = 6.7 Hz), 5.00 (sept, 1 H, J = 6.7 Hz), 7.39 (ddd, 1 H, J = 7.9, 6.7, 1.2 Hz), 7.56 (d, 1 H, J = 7.9 Hz), 7.59 (ddd, 1 H, J = 7.9, 6.7, 1.2 Hz), 8.03 (d, 1 H, J = 7.9 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ = 22.2, 46.0, 120.4, 125.3, 125.5, 126.5, 131.5, 140.1, 164.8.

MS: m/z (%) = 193 (M^+), 178, 151 (100), 123, 96, 69.

2-Cyclopropyl-1,2-benzisothiazolin-3-one (2e)

Colorless oil.¹³

IR (neat): 1657 (C=O), 1449, 1333, 741, 673 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.05–1.12 (m, 4 H), 3.10–3.17 (m, 1 H), 7.38 (ddd, 1 H, J = 8.0, 6.9, 1.1 Hz), 7.50 (dt, 1 H, J = 8.0, 0.8 Hz), 7.60 (ddd, 1 H, J = 8.0, 6.9, 1.4 Hz), 8.01 (ddd, 1 H, J = 8.0, 1.4, 0.8 Hz).

MS: m/z (%) = 191 (M^+), 137, 136 (100), 108, 82, 69.

2-(tert-Butyl)-1,2-benzisothiazolin-3-one (2f)

Chromatographed with CH_2Cl_2 -acetone-MeOH (100:5:1) mixture as an eluent; colorless oil.¹¹

IR (neat): 1651 (C=O), 1451, 1302, 1206, 741, 675 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 1.71 (s, 9 H), 7.37 (ddd, 1 H, J = 8.0, 6.9, 1.1 Hz), 7.50 (ddd, 1 H, J = 8.0, 1.1, 0.8 Hz), 7.57 (ddd, 1 H, J = 8.0, 6.9, 1.3 Hz), 7.97 (ddd, 1 H, J = 8.0, 1.3, 0.8 Hz).

MS: m/z (%) = 207 (M^+), 152, 151 (100), 123, 108, 96.

2-(2-Phenyl-2-propyl)-1,2-benzisothiazolin-3-one (2g)

Chromatographed with CH_2Cl_2 as an eluent; white crystals; mp 131–132 °C (EtOAc-hexane) (Lit.¹¹ mp 131–132 °C).

IR (KBr): 1638 (C=O), 1445, 1327, 1179, 745, 698 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 2.06 (s, 6 H), 7.29–7.43 (m, 6 H), 7.48 (ddd, 1 H, J = 8.0, 1.1, 0.8 Hz), 7.58 (ddd, 1 H, J = 8.0, 7.1, 1.1 Hz), 7.92 (ddd, 1 H, J = 8.0, 1.3, 0.8 Hz).

MS: m/z (%) = 269 (M^+), 151 (100), 119, 118, 103, 91, 77.

2-(p-Methylphenyl)-1,2-benzisothiazolin-3-one (2h)

White crystals; mp 136.7–137.1 °C (benzene-hexane) (Lit.¹³ mp 136.7–137.1 °C).

IR (KBr): 1642 (C=O), 1505, 1447, 1331, 1127, 750 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 2.39 (s, 3 H), 7.28 (d, 2 H, J = 8.2 Hz), 7.45 (ddd, 1 H, J = 8.0, 6.9, 1.1 Hz), 7.55–7.60 (m, 3 H), 7.66 (ddd, 1 H, J = 8.0, 6.9, 1.1 Hz), 8.11 (dt, 1 H, J = 8.0, 1.1 Hz).

MS: m/z (%) = 241 (M^+ , 100), 226, 208, 198, 136, 120, 108, 91, 69.

2-(p-Methoxyphenyl)-1,2-benzisothiazolin-3-one (2i)

White crystals; mp 147–148 °C (EtOH) (Lit.¹³ mp 147–148 °C).

IR (KBr): 1659 (C=O), 1507, 1443, 1242, 1019, 839, 749 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 3.84 (s, 3 H), 6.98 (d, 2 H, J = 9.2 Hz), 7.44 (td, 1 H, J = 7.6, 1.2 Hz), 7.54 (d, 2 H, J = 9.2 Hz), 7.57 (d, 1 H, J = 8.3 Hz), 7.65 (ddd, 1 H, J = 8.3, 7.6, 1.1 Hz), 8.09 (dd, 1 H, J = 7.6, 1.1 Hz).

MS: m/z (%) = 257 (M^+ , 100), 242, 214, 186, 136, 108, 69.

Methyl (3-Oxo-1,2-benzisothiazol-2-yl)acetate (2j)

Chromatographed with CH_2Cl_2 -acetone-MeOH (100:5:1) mixture as an eluent; white crystals; mp 92.2–93.2 °C (EtOAc-hexane).

IR (KBr): 2980, 2361, 1742 (C=O), 1667 (C=O), 1449, 1431, 1399, 1370, 1345, 1290, 1223, 1069, 970, 747 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 3.79 (s, 3 H), 4.63 (s, 2 H), 7.42 (td, 1 H, J = 7.0, 0.9 Hz), 7.57 (d, 1 H, J = 7.9 Hz), 7.64 (ddd, 1 H, J = 8.2, 7.0, 1.2 Hz), 8.06 (dd, 1 H, J = 7.9, 0.9 Hz).

^{13}C NMR (125 MHz, CDCl_3): δ = 44.5, 52.7, 120.4, 123.4, 125.7, 127.0, 132.3, 140.9, 165.8, 168.2.

MS: m/z (%) = 223 (M^+), 164 (100), 136, 108, 82, 69.

Anal. Calcd for $\text{C}_{10}\text{H}_9\text{NO}_3\text{S}$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.96; H, 3.83; N, 6.08.

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