Process Development of 1,2-Benzisothiazolin-3(*2H*)-one by Replacing of the Toxic Materials

Chun Keun Jin,[b] Jung-Kyen Moon,[1] Woo Song Lee,*[a] Keun Soo Nam*[b]

[a] Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Daejeon 305-333, Republic of Korea
Fax +82(42)8612675; E-mail: wslee@kribb.re.kr

[b] NeoNal Company, Ltd., Pyungchon, Seo-ku, Daejeon 302-070, Republic of Korea

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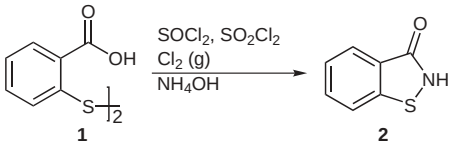
Abstract: 1,2-Benzisothiazolin-3(*2H*)-one (**2**) was synthesized by 2,2′-dithiodibenzoic acid (**1**) with acetamide or urea in high yield via one-pot amidation-cyclization process.

Key words: 1,2-benzisothiazolin-3(2*H*)-one, amidation-cyclization, one-pot-procedure

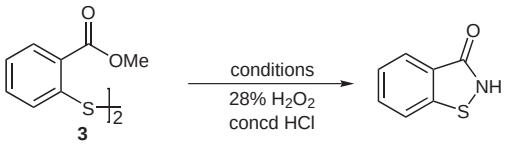
1,2-Benzisothiazolin-3(*2H*)-one (**2**) was first synthesized by McKibben and McClelland in 1923.[2] Since that time, it has been discovered that structure **2** possesses high antibacterial and antifungal activity.[3] In general, synthetic routes to **2** require halogenation of acid chloride, amidation, and cyclization with some manipulations, starting from 2,2′-dithiodibenzoic acid (**1**),[4] thiosalysilic acid,[5] and others.[6] Although these known methods have been proven to be useful protocols, they are of limited use for producing compound **2** because of problem using highly toxic agents and still remaining of chlorine in final compound **2** (Scheme 1). Our purpose for improving these problems is to avoid use of highly toxic chlorine. In this paper, we report process development of 1,2-benzisothiazolin-3(*2H*)-one **2** by replacing of the toxic materials, starting from 2,2′-dithiodibenzoic acid (**1**).



Scheme 1

2,2′-Dithiodibenzoate (**3**) was synthesized from the reaction of commercially available **1** with Me_2SO_4 in 5% NaOH solution. Subsequently, treatment of **3** with 2.4 equivalents of acetamide and MeONa in toluene under reflux condition for 3 hours to give the 1,2-benzisothiazolin-2(*3H*)-one (**2**) in 90% yield. When 3.0 equivalents of acetamide and sodium methoxide has been used, the chemical yield was not changed, except for shorter reaction time. Based on above reaction conditions using acetamide to be an amine source, similar treatment of **3** with more cheaper urea economically gave compound **2** in 75% yield with impurity, which required refine process in final step giving pure compound **2** (Table 1).

Table 1 Solvents and Equimolar Effects in One-Pot Amidation-Cyclization Process



Entry	Equiv of A.A.[a] or U[b]	Equiv of NaOMe	Solvents	Temp (°C)	Time (h)	Yield (%)[c]
1	A.A. (2.4)	2.4	Toluene	80	3	90
2	A.A. (3.0)	3.0	Toluene	80	2	90
3	U (2.4)	2.4	Toluene	80	3	75
4	U (3.0)	3.0	Toluene	80	2	80
5	A.A. (2.4)	2.4	Chlorobenzene	80	5	75

[a] A.A. = acetamide.
[b] U = urea.
[c] Isolated yield.

Also, chlorobenzene has been found to be an acceptable solvent for amidation. However, this solvent required refine process in final step to obtain the compound **2** and resulted in a low yield. As shown in Table 1, the optimum reaction conditions involved toluene solvent to improve reactivity and affording mild and clean amidation, which was subjected to cyclization under H_2O_2 giving the desired 1,2-benzisothiazolin-3(*2H*)-one (**2**) in high yield without further purification.[7]

Then, the structure of compound **2** was determined on the basis of their characteristic spectroscopic data and authentic sample which was reported in several literatures.[4–6] The purity of compound **2** was has proven to be 99.3% by HPLC analysis.[8]

The most likely mechanism for the formation of **2** from **3** may be rationalized in terms of the sequential pathway (Scheme 2: **4**→**5**→**6**→**7**→**8**→**2**),[9,10] namely, sodium acetamide attacks methyl ester carbon of **3** giving 2,2′-dithiodibenzamide (**4**), which was oxidized in situ by electrophilic oxidant, H_2O_2, to give thiolsulfinate **5**. Then, the thiolsulfinate **5** was cyclized to produce 2-acetylbenzo[*d*]isothiazol-3-one (**7**) and sufanyl compound **6**

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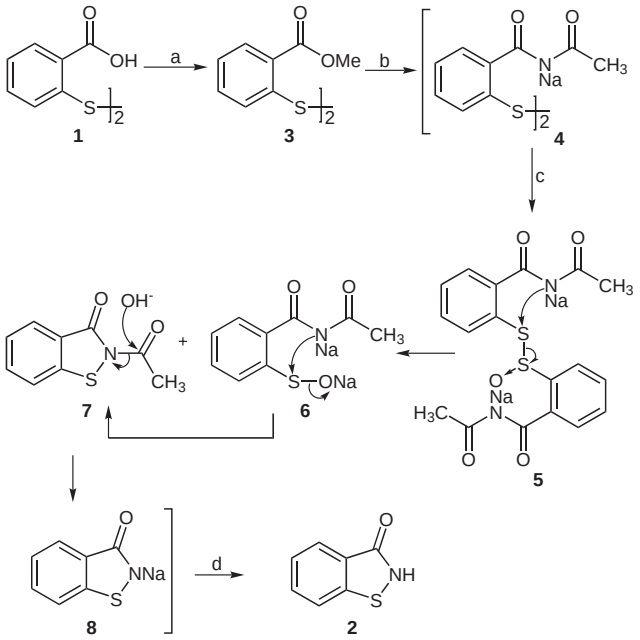

Scheme 2 *Conditions*: a) $MeSO_4$, 5% NaOH, 25 °C, 3 h; b) CH_3CONH_2, NaOMe, toluene, reflux, 3 h; c) 28% H_2O_2, 50 °C, 30 min; d) concd HCl, 25 °C.

that immediately undergoes cyclization giving **7**, eventually affording the intermediate **8**. The intermediate **8** was acidified with concd HCl to give the compound **2** as off-white solid (Scheme 2).

In conclusion, we found a simple and economical process for producing 1,2-benzisothiazolin-3(*2H*)-one (**2**) on an industrial scale, without using materials that are costly and dangerous in handling.

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(7) Procedure of 1,2-Benzisothiazolin-3(*2H*)-one (**2**).[11]
To a 1000 L reactor was equipped with a mechanical stirrer, a thermometer, and a condenser, 28% NaOMe (52.1 kg) in MeOH solution was added for 10 min and distilled under reduced pressure (60 °C/750 mmHg, 2.5 h) to get the MeOH (15 L). In order to get rid of the extra MeOH, toluene (100 kg) was added and distilled to get the MeOH (15 L) for 1.5 h. Acetamide (16 kg) was added and refluxed for 1 h, then, the reactor was cooled to 25 °C. Dimethyl 2,2′-dithiodibenzoate (**3**) (23.5 kg) was slowly added at 25 °C, the reaction mixture was refluxed at 80 °C for 2 h, cooled to <20 °C, added H_2O (150 L), stirred for 30 min, filtered, and separated to give aqueous layer and toluene layer (70 kg). The aqueous layer was added 28% H_2O_2 (12 kg) dropwisely for 30 min (increasing temperature to 50–55 °C). The basic active carbon (3 kg) and Al_2O_3 (DN-3) (300 g) were added, stirred for 1 h at 25 °C, and filtered. Addition of conc. HCl (20 kg, 35% solution, and pH = 3–4) was added dropwisely to precipitate the wet 1,2-benzisothiazolin-3(*2H*)-one (**2**), which was filtered, washed with cold water (30 L), and dried on air to afford **2** (18 kg, 85%) as off-white solid (MeOH), mp 157–158 °C (lit.[12] mp 158–159 °C).
IR (KBr): 3420, 3056, 2911, 1630 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 5.70 (br s, 1 H), 6.53 (d, 1 H, *J* = 1.7 Hz), 7.37–7.62 (m, 5 H), 11.64 (br s, 1 H).
Anal. Calcd for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.45; H, 3.50; N, 9.52; S, 21.08.

(8) The purity of **2** was verified by HPLC analysis employing the Shimadzu LC-6A instrument equipped with an SPD-6A UV detector as follows: Compound **2**: Detector, Youngjin M 720; pump, waters 510; integrator, waters 746, Youngjin D 520B; wave length, UV-225 nm, column, ODS-2 (250 nm × 4.6Ψ); end time, 30 min; eluent MeOH–H_2O (35:65, v/v); flow rate, 1.0 mL/min; attenuation, 1.28; chart speed, 0.5. Procedure is as follows: 10 mg standard 1,2-benzisothiazolin-3(*2H*)-one (BIT) (**2**) is weighed to 0.1 mg accuracy in 100 mL flask and added 10 mL of 0.5 (w/v)% methylbenzoate/MeOH. The flask is filled up with HPLC eluent to 100 mL. Compound **2** is prepared as same as standard BIT. At least three HPLC tests are conducted until constant areas are obtained. Compound **2** assay is calculated from the HPLC area in proportion to standard BIT. Calculation was conducted as follows: Compound **2** assay = (the area of compound **2** ≥ the area of methylbenzoate)/(the area of standard BIT ≥ the area of methylbenzoate) × 100.

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