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PREPARATION OF BENZISOTHIAZOLONES FROM 2-BROMOBENZAMIDES AND SULFUR UNDER COPPER CATALYSIS CONDITIONS

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A convenient two-stage method has been developed for preparing benz[d]isothiazol-3(2H)-ones from 2-bromobenzamides and sulfur in a one-pot process under copper catalysis conditions. The method is suitable for the synthesis of N-aryl-, benzyl-, and alkyl-substituted benzisothiazolones. The yields of the benzisothiazolones depend on the nature of the starting amide and can reach 91%.

Keywords: benzisothiazolone, 2-bromobenzamide, sulfur, copper catalysis, S–N bond.

Benzisothiazolone derivatives are widely used in medicine, agriculture, and in the food industry. For example, Landromil is an antifungal medication [1], Proxel PL is used as a pesticide [2], and the oxidized form of a benzisothiazolone (saccharin) is the food additive E954. In addition, a benzisothiazolone fragment is present in many potential medicinal preparations [3-6].

The main method for synthesizing benzisothiazolones is based on a reaction of 2-mercaptobenzoic acid derivatives, such as benzamides [7-9], sulfinylbenzamides [10, 11], and 2,2'-disulfanediylbenzoic acids [1, 12-18]. In theory, the most rational option for the benzisothiazolone N–S–C bond formation is the use of elemental sulfur as reagent. Several examples are known for using sulfur to form thiol derivatives in copper-catalyzed reactions [19-22]. Recently methods for synthesis of benzisoselenazolones [23] and benzisothiazolones [24] from 2-halobenzamides and selenium or sulphur, respectively, under copper catalysis conditions have been reported. The yields of benzisothiazolones amounted to 40-95%, but there was no general conditions reported in the publication [24] for carrying out this synthesis. In addition, it was necessary to use 2-iodobenzamides and a great amount of catalyst and ligand (25-100 mol%) for a successful reaction.

The aim of our investigation was development of a method for preparing benzisothiazolone derivatives from the more available 2-bromobenzamides and sulfur.

The cyclization of *N*-benzyl-2-bromobenzamide (**1a**) was initially carried out in the presence of sulfur under the conditions used for the synthesis of benzisoselenazolones (10 mol% CuI and 1,10-phenanthroline, 1.5 equiv. K_2CO_3, DMF, 110°C, 24 h [23]).

The initial experiments indicated that full conversion of the starting amide **1a** did not occur over the course of the reaction; moreover, a mixture was formed of the benzisothiazolone **2a** (8%), disulfide **3a** (4%), and the mono- and polysulfides **4a**.

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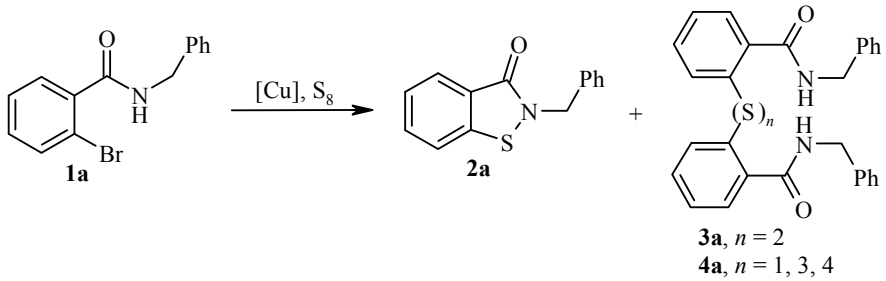
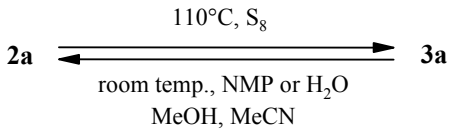


The benzamide **1a** cyclization reaction was carried out using different solvents: acetonitrile, dioxane, toluene, DMSO, water, and *N*-methylpyrrolidone (NMP). Full conversion of the starting material was reached only in NMP, but the yield of compound **2a** in this case was not more than 28%. At a lower (90°C) or higher (130°C) temperature the disulfide **3a** was formed exclusively, instead of the expected benzisothiazolone **2a**. Various combinations of copper sources (CuCl, CuBr, CuI, Cu_2O, CuO, $Cu(OAc)_2$, Cu), ligands (phenanthroline, neocuproine, diphenylphosphine, 2,2'-bipyridine, isobutylcyclohexanone, salicylaldoxime), and bases (AcONa, *t*-BuONa, AcOK, K_2CO_3, Cs_2CO_3) were explored. The yield of the cyclization product was increased with the use of 2,2'-bipyridine and reached 38%. In turn, an increase in the quantity of K_2CO_3 to 3 equivalents in the presence of phenanthroline gave a 70% yield of the benzisothiazolone **2a**.

Full conversion of the 2-bromobenzamide **1a** required 24 h and gave a 70% yield of the benzisothiazolone **2a**. Decreasing the reaction time to 18 h lowered the yield to 48%, while a longer heating of the reaction mixture (48 h) gave the disulfide **3a** as the sole product, due to dimerization of the compound **2a**. The dimerization side reaction therefore prevents obtaining a quantitative yield of the benzisothiazolone **2** under the given reaction conditions.

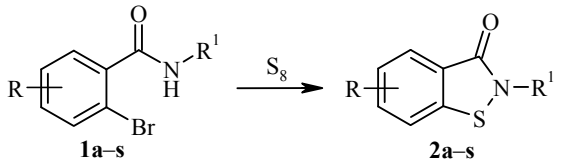


Within the scope of this investigation we also studied the stability of the benzisothiazolone **2a** and the disulfide **3a**. We found an equilibrium between compound **2a** and the corresponding side product **3a**, which was shifted under the influence of temperature and in the presence of sulfur. At room temperature the equilibrium favored the formation of benzisothiazolone **2a**, while an increase in temperature or addition of sulfur led to the formation of disulfide **3a**.

According to literature information, the disulfide **3** could cyclize to the benzisothiazolone **2a** in the presence of oxidants, such as *O*-methylhydroxylamine [12], chlorine [13], or bromine [15]. When carrying out the reaction of the 2-bromobenzamide **1a** with sulfur, K_2CO_3, CuI, ligand, and *O*-methylhydroxylamine, the ^{1}H NMR spectrum of reaction mixture showed an increase in the amount of benzisothiazolone **2a** compared to the disulfide **3a**, but with a sharply decreased conversion of the starting compound **1a**. Hence we decided to initially carry out the copper-catalyzed reaction to full conversion of the substrate and then to treat the reaction mixture with *O*-methylhydroxylamine. With the use of phenanthroline as ligand, the yield remained as before at around 70%, while in the presence of 2,2'-bipyridine the 2-benzylbenzisothiazolone was obtained in 94% yield.

Hence, in the course of this work we found two methods for the preparation of benzisothiazolones from 2-bromobenzamides and sulfur under copper-catalyzed conditions; the method A was a two-stage one-pot synthesis, the first stage of which occurred in the presence of 10 mol% of CuI and 2,2'-bipyridine, and in the second stage the reaction mixture was treated with *O*-methylhydroxylamine to prepare the benzisothiazolones; the method B was a one-stage synthesis without hydroxylamine treatment, and with 1,10-phenanthroline as ligand.

Both methods were used to prepare a variety of substituted benzisothiazolones, in order to establish their scope and limitations.



1a–s **2a–s**

1, **2 a-m** R = H, **a** R^1 = Bn, **b** R^1 = H, **c** R^1 = Me, **d** R^1 =Bu, **e** R^1 = *t*-Bu, **f** R^1 = 4-$MeOC_6H_4CH_2$,
g R^1 = 4-$F_3COC_6H_4CH_2$, **h** R^1 = 4-$FC_6H_4CH_2$, **i** R^1 = 2-$F_3CC_6H_4CH_2$, **j** R^1 = 4-MeC_6H_4, **k** R^1 = 4-$MeOC_6H_4$,
l R^1 = 4-$F_3CC_6H_4$, **m** R^1 = 4-BrC_6H_4; **n** R = 5-NO_2, R^1 = Bn; **o** R = 5-MeO, R^1 = Bn; **1p** R = 4,5-$(MeO)_2$,
2p R = 5,6-$(MeO)_2$, **1q** R = 4-F, **2q** R = 6-F, **1r** R = 3-Me, **2r** R = 7-Me,
1s R = 4-CONHBn, **2s** R = 6-CONHBn, **1**, **2 p-s** R^1 = Bn

When carrying out the reactions by method A, the yield of the benzisothiazolone **2b** from cyclization of 2-bromobenzamide **1b** was low (15%, Table 1). Compound **2b** was not observed at all in the conditions of method B, which indicates that primary benzamides are not suitable substrates. In the series of *N*-alkyl- and *N*-benzylbenzamides **1a,c-i**, the yields of the benzisothiazolones **2a**,**c-i** (66-94%) did not depend on the nature of the substituents at the nitrogen atom and in the phenyl ring of the benzyl group. The 2-arylbenzisothiazolones **2j-m** were prepared in 26-80% yields. The presence of an electron-withdrawing group in the phenyl ring decreased the reaction product yield, while an electron-donating group increased it. This was illustrated by the yields of the 2-(4-tri-fluoromethylphenyl)- (**2l**) and 2-(4-methoxyphenyl)benz[*d*]isothiazolone (**2k**) (26 and 72%, respectively). The low yield of the 2-(4-bromophenyl)benzisothiazolone **2m** was associated with side reactions occurring at the bromine atom in the benzene ring. It was also shown that di-*ortho*-substituted bromides were suitable substrates, as evidenced by the high yield (80%) of the 7-methyl-benzisothiazolone **2r**. The method permitted the use of substrates with other amide groups in the benzamide ring, as demonstrated by the high yield (87%) of compound **2s** (Table 1).

TABLE 1. Characteristics of the Synthesized Compounds **2a-s**

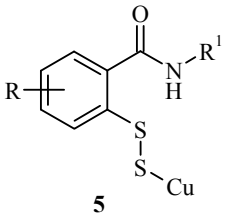
Compound	Crystal color	Mp, °C		Yield, %	
		Found	Literature data	Method A	Method B
2a	White	84-85	79–80 (EtOH) [24]	94	70
2b	White	152-153	150–151 [18]	15	0
2c	White	49-50	46–47 [18]	67	32
2d	Yellow	137-138	144–147 [24]	82	—
2e	Orange	58-59	57–58 [25]	66	—
2f	Orange	74-75	75.2–76.3 (EtOH) [26]	84	58
2g	Yellow	98-97	—	67	27
2h	Orange	90-91	—	72	33
2i	White	85-87	—	77	—
2j	Yellow	134-135	137 [27]	80	42
2k	White	140-141	148–149 [8]	72	60
2l	Yellow	189-190	—	26	31
2m	Orange	128-129	128–130 [24]	28	—
2n	Yellow	137-138	138–141 [24]	50	22
2o	Yellow	71-72	68–70 [24]	89	77
2p	Yellow	166-167	—	81	—
2q	Orange	116-117	—	49	—
2r	White	65-66	66–68 [24]	80	—
2s	White	170-171	—	87	—

TABLE 2. Elemental Analysis Data for the Synthesized Benzisothiazolones **2g**,**h**,**i**,**p**,**q**,**s**

Compound	Empirical formula	Found, % / Calculated, %			
		C	H	N	S
2g	$C_{15}H_{10}F_3NO_2S$	55.05 / 55.38	3.28 / 3.10	4.27 / 4.31	9.49 / 9.86
2h	$C_{14}H_{10}FNOS$	64.91 / 64.85	3.92 / 3.89	5.40 / 5.40	12.47 / 12.37
2i	$C_{15}H_{10}F_3NOS$	58.21 / 58.25	3.33 / 3.26	4.66 / 4.53	10.17 / 10.37
2p	$C_{16}H_{15}NO_3S$	64.03 / 63.77	5.12 / 5.02	4.75 / 4.65	10.91 / 10.64
2q	$C_{14}H_{10}FNOS$	64.50 / 64.85	3.87 / 3.89	5.45 / 5.40	12.41 / 12.37
2s	$C_{22}H_{18}N_2O_2S$	70.25 / 70.57	4.76 / 4.85	7.48 / 7.48	8.21 / 8.56

In almost all cases the method B gave a lower yield, with the exception of the 2-(4-trifluoromethylphenyl)benz[*d*]isothiazol-3(2*H*)-one (**2l**). In this case the yield was about 30% by both methods.

We propose that the reaction course depends on the choice of ligand. It is possible that upon the use of 2,2'-bipyridine, an Ar–S bond forms initially, and this gives the disulfide **3** *via* the intermediate complex **5**. Then treatment with the *O*-methylhydroxylamine leads to cyclization of disulfide **3** to give two molecules of the benzisothiazolone **2** [12]. In turn, in the presence of 1,10-phenanthroline apparently an N–S bond is first created, and then compound **2** is formed from complex **6** according to the previously proposed mechanism for the synthesis of benzisoselenazolones [23]. If the disulfide **3** were the only intermediate, the maximum yield of the benzisothiazolone without addition of *O*-methylhydroxylamine would be 50%.



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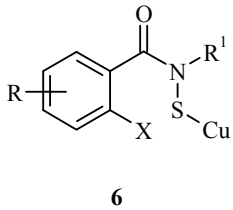

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Hence we have developed a two-stage, one-pot method for preparing benzisothiazolones from 2-bromobenzamides and elemental sulfur in the presence of a copper catalyst.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu Prestige-21 IR spectrometer using KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (400 and 100 MHz, respectively) using DMSO-d_6 with the residual solvent signals as internal standard (2.50 ppm for the ^1H nucleus and 39.5 ppm for the ^{13}C nucleus). Elemental analysis was performed on a Carlo Erba 1108 analyzer; melting points were determined on an Optimelt instrument. Column chromatography used Acros silica gel (0.06-0.20 mm).

The benzamides **1b**,**h**,**k**, substituted benzoic acids, and the benzoyl chlorides were commercially available reagents.

TABLE 3. Spectroscopic Parameters of the Benzisothiazolones **2g**,**h**,**i**,**p**,**q**,**s**

Compound	IR spectrum, ν, cm^{-1} (C=O)	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	^{13}C NMR spectrum δ, ppm
2g	1639	5.07 (2H, s, NCH_2); 7.33-7.40 (2H, m, H-3,5 Ar); 7.42-7.49 (3H, m, H-5, H-2,6 Ar); 7.65-7.72 (1H, m, H-6); 7.98-7.88 (2H, m, H-4,7)	45.9; 119.2; 121.7; 122.5; 124.3; 126.1; 126.2; 130.3; 132.5; 136.9; 141.1; 148.3; 164.9
2h	1635	5.02 (2H, s, NCH_2); 7.15-7.23 (2H, m, H-2,6 Ar); 7.35-7.48 (3H, m, H-5, H-3,5 Ar); 7.64-7.71 (1H, m, H-6); 7.87-7.98 (2H, m, H-4,7)	46.0; 115.8; 116.0; 122.4; 126.0; 126.2; 130.6; 130.7; 132.4; 133.7; 141.0; 164.8
2i	1668	5.20 (2H,s, NCH_2); 7.36 (1H, d, *J* = 7.8, H-6 Ar); 7.47 (1H, dt *J* = 7.8, *J* = 0.7, H-4 Ar); 7.51-7.59 (1H, m, H-7); 7.64-7.74 (2H, m, H-6, H-3 Ar); 7.80 (1H, d, *J* = 7.8, H-7); 7.91-8.01 (2H, m, H-4, H-5 Ar)	45.7; 124.4; 126.3; 128.3; 128.5; 128.8 (2C); 131.1; 132.2; 134.7; 135.8; 137.6 (2C); 143.3; 167.2
2p	1666	3.81-3.87 (6H, m, $2OCH_3$); 4.99 (2H, s, NCH_2); 7.26-7.39 (6H, m, H-7, H Ph); 7.50 (1H, s, H-4)	46.7; 56.2; 56.4; 103.9; 106.8; 116.6; 128.1; 128.2; 129.1; 134.4; 137.6; 148.8; 153.6; 164.9
2q	1626	5.01 (2H, s, NCH_2); 7.26-7.40 (6H, m, H-5,7, H-2,3,5,6 Ph); 7.82 (1H, dd, *J* = 9.0, *J* = 2.4, H-4 Ph); 7.94 (1H, dd, *J* = 8.6, *J* = 5.5, H-4)	46.9; 109.2; 114.8; 121.2; 128.3; 128.5 (2C); 128.6; 129.2; 137.2; 143.1; 164.0
2s	1544, 1641	4.50 (2H, d, *J* = 5.8, $NHC\underline{H}_2$); 5.05 (2H, s, NCH_2); 7.18-7.42 (10H, m, H Ph); 7.89 (1H, dd, *J* = 8.2, *J* = 1.4, H-5); 7.99 (1H, d, *J* = 8.2, H-4); 8.42-8.45 (1H, m, H-7); 9.25 (1H, t, *J* = 5.8, $N\underline{H}CH_2$)	43.3; 46.9; 122.2; 124.6; 126.2 (2C); 127.3; 127.7; 128.3; 128.4; 128.7; 129.2; 137.2; 138.3; 139.8; 141.2; 164.3; 166.1

Synthesis of 2-Bromobenzamides (1a,c-g,i,j,l-s). The benzamides **1a**,**c-g**,**i**,**j**,**l-o**,**r** were prepared by known methods [28] and [29], and the benzamides **1p**,**q**,**s** by method [30]. The compounds obtained are white, crystalline materials (with the exception of amide **1m**). The spectroscopic parameters of the known compounds **1a**,**c**,**d**,**f**,**j**,**l**,**n-r** agreed with literature data.

***N*-Benzyl-2-bromobenzamide (1a)**. Yield 98%; mp 114-116°C (EtOH) (mp 115-117°C [31]).

2-Bromo-*N*-methylbenzamide (1c). Yield 78%; mp 142-144°C (EtOH) (mp 142°C (EtOH) [32]).

2-Bromo-*N*-butylbenzamide (1d). Yield 80%; mp 92-93°C (EtOH) [33].

2-Bromo-*N*-*tert*-butylbenzamide (1e). Yield 87%; mp 110-111°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (9H, s, $C(CH_3)_3$); 7.28-7.42 (3H, m, H-3,4,5); 7.58-7.63 (1H, m, H-6); 7.95 (1H, br. s, CONH). ^{13}C NMR spectrum, δ, ppm: 28.9; 51.3; 119.4; 127.8; 129.0; 130.7; 132.9; 140.6; 167.2. Found, %: C 51.58; H 5.42; N 5.40. $C_{11}H_{14}BrNO$. Calculated, %: C 51.58; H 5.51; N 5.47.

2-Bromo-*N*-(4-methoxybenzyl)benzamide (1f). Yield 85%; mp 104-105°C (EtOH) [34].

2-Bromo-*N*-(4-trifluoromethoxybenzyl)benzamide (1g). Yield 90%; mp 113-114°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.51 (2H, d, *J* = 5.9, $NHC\underline{H}_2$); 7.27-7.37 (3H, m, H-5, H-2,6 Ar); 7.43 (1H, d, *J* = 7.9, H-4); 7.47-7.53 (2H, m, H-3,5 Ar); 7.63 (1H, d, *J* = 8.4, H-3); 7.75 (1H, d, *J* = 7.3, H-6); 9.32 (1H, t, *J* = 5.9, CONH). ^{13}C NMR spectrum, δ, ppm: 42.2; 119.3; 121.4; 121.8; 128.1; 129.3; 129.6; 131.4; 133.2; 139.1; 139.4; 147.7; 167.8. Found, %: C 48.07; H 2.89; N 3.61. $C_{15}H_{11}BrF_3NO_2$. Calculated, %: C 48.15; H 2.96; N 3.74.

2-Bromo-*N*-(2-trifluoromethylbenzyl)benzamide (1i). Yield 89%; mp 112-113°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.63 (2H, d, *J* = 5.8, $NHC\underline{H}_2$); 7.39 (1H, m, H-6 Ar); 7.43-7.54 (3H, m, H-5, H-3,4

Ar); 7.65-7.78 (4H, m, H-3,4,6, H-5 Ar); 9.08 (1H, t, *J* = 5.8, CONH). ^{13}C NMR spectrum, δ, ppm: 39.3; 119.3; 126.1; 126.2; 127.9; 128.1; 129.0; 129.3; 131.5; 133.1; 133.2; 137.5 (2C); 139.2; 168.0. Found, %: C 50.49; H 2.97; N 3.81. $C_{15}H_{11}BrF_3NO$. Calculated, %: C 50.30; H 3.10; N 3.91.

2-Bromo-*N*-(4-methylphenyl)benzamide (1j). Yield 91%; mp 147-148°C (EtOH) (mp 146.5-147.5°C (hexane) [30]).

2-Bromo-*N*-(4-trifluoromethylphenyl)benzamide (1l). Yield 85%; mp 124-125°C (EtOH) (mp 121-122°C [35]).

2-Bromo-*N*-(4-bromophenyl)benzamide (1m). Yield 90%. Yellow crystals; mp 146-148°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.39-7.46 (1H, m, H-5); 7.47-7.59 (4H, m, H-3,4,3',5'); 7.67-7.75 (3H, m, H-6,2',6'); 10.62 (1H, s, CONH). ^{13}C NMR spectrum, δ, ppm: 115.9; 119.4; 121.9; 128.2; 129.3; 131.8; 132.1; 133.2; 138.7; 139.3; 166.3. Found, %: C 44.11; H 2.50; N 3.82. $C_{13}H_9Br_2NO$. Calculated, %: C 43.98; H 2.56; N 3.95.

***N*-Benzyl-2-bromo-5-nitrobenzamide (1n)**. Yield 60%; mp 202-205°C (EtOH) [25].

***N*-Benzyl-2 -bromo-5-methoxybenzamide (1o)**. Yield 64%; mp 114-115°C (EtOH) [33].

***N*-Benzyl-2-bromo-4,5-dimethoxybenzamide (1p)**. Yield 76%; mp 156-157°C (EtOH) [25].

***N*-Benzyl-2-bromo-4-fluorobenzamide (1q)**. Yield 72%; mp 137-138°C (EtOH) [25].

***N*-Benzyl-2-bromo-3-methylbenzamide (1r)**. Yield 99%; mp 101-102°C (EtOH) [25].

***N*^{1},*N*^{4}-Dibenzyl-2-bromoterephthalamide (1s)**. Yield 86%; mp 206-207°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.21-7.29 (2H, m, 2H-4 Ph); 7.31-7.41 (8H, m, 2H-2,3,5,6 Ph); 7.44-7.51 (4H, m, 2NHC<u>H</u>$_2$); 7.53 (1H, d, *J* = 8.0, H-6); 7.98 (1H, dd, *J* = 8.0, *J* = 1.6, H-5); 8.18 (1H, d, *J* = 1.6, H-3); 9.08 (1H, t, *J* = 6.0, CONH); 9.35 (1H, t, *J* = 6.0, CONH). ^{13}C NMR spectrum, δ, ppm: 42.9; 43.2; 119.4; 127.0; 127.3 (2C); 127.6; 127.7; 128.7; 129.2; 131.8; 133.9; 136.7; 139.4; 139.7; 141.7; 164.6; 167.5. Found, %: C 62.32; H 4.32; N 6.52. $C_{22}H_{19}BrN_2O_2$. Calculated, %: C 62.42; H 4.52; N 6.62.

Benzisothiazolones 2a-s (General Method). A. NMP (1 ml) was added to CuI (10 mg, 0.05 mmol) and 2,2'-bipyridine (8 mg, 0.05 mmol) under an argon stream and stirred for 10 min. Sulfur (24 mg, 0.75 mmol), the 2-bromobenzamide **1a-s** (0.50 mmol), and K_2CO_3 (207 mg, 1.50 mmol) were added. The reaction vessel was closed with a teflon stopper, and the reaction mixture was stirred for 24 h at 110°C. *O*-Methyl-hydroxylamine hydrochloride (84 mg, 1.00 mmol) and dry pyridine (0.16 ml, 2.00 mmol) were added under the argon stream. The reaction mixture was stirred for 3 h at 110°C, cooled, filtered through celite, a 0.1 M HCl solution (5 ml) was added, and the product was extracted with EtOAc. The organic layer was separated and washed with water and saturated NaCl solution. The extract was dried over Na_2SO_4, and evaporated *in vacuo*. The product was purified by column chromatography using hexane–ethyl acetate (8:1) as eluent.

B. NMP (1 ml) was added to CuI (10 mg, 0.05 mmol) and 1,10-phenanthroline (8 mg, 0.05 mmol) under an argon stream and stirred for 10 min. Sulfur (24 mg, 0.75 mmol, 1.5 eq.), the 2-bromobenzamide **1a-s** (0.50 mmol), and K_2CO_3 (207 mg, 1.50 mmol) were added. The reaction vessel was closed with a teflon stopper, and the reaction mixture was stirred for 24 h at 110°C, cooled, filtered through celite, a 0.1 M HCl solution (5 ml) was added, and the product was extracted with EtOAc. The organic layer was separated and washed with water and saturated NaCl solution. The extract was dried over Na_2SO_4, and evaporated *in vacuo*. The product was purified by column chromatography using hexane–ethyl acetate (8:1) as eluent.

The spectroscopic parameters for the known benzisothiazolones **2a-f**,**j-o**,**r** agreed with literature data.

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