HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 444 - 451. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 6th July, 2019, Accepted, 5th August, 2019, Published online, 1st October, 2019
DOI: 10.3987/COM-19-S(F)46

SYNTHESIS OF 2-AMINO-1,3-BENZOSELENAZOLE VIA METAL-FREE CYCLIZATION FROM ISOTHIOCYANATE AND BIS(*o*-AMINOPHENYL)DISELENIDE

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This manuscript is in celebration of Professor Kaoru Fuji's 80th birthday.

Abstract – Amino-1,3-benzoselenazoles were generated from the reactions of bis(*o*-aminophenyl)diselenide and various isothiocyanates under metal-free cyclization conditions. The cyclization of isothiocyanate bearing bulky substituents proceeded in excellent yields because the amounts of byproducts generated were reduced. Acid hydrolysis of acetamide produced 2-amino-1,3-benzoselenazole (**4**).

Benzothiazole, a bioisostere of benzoxazole, is one of the most attractive heterocycles found in pharmaceuticals, agricultural chemicals, natural products, and materials chemistry.[1] Particularly, 2-amino-1,3-benzothiazole is responsible for several biological and pharmacological properties. Examples include Riluzole, herbicidal activity against both dicotyledon and monocotyledon weeds, and monoazo disperse dye, and derivatizations have paved the way for the wide use of these compounds as intermediates in organic synthesis (Figure 1).[2]

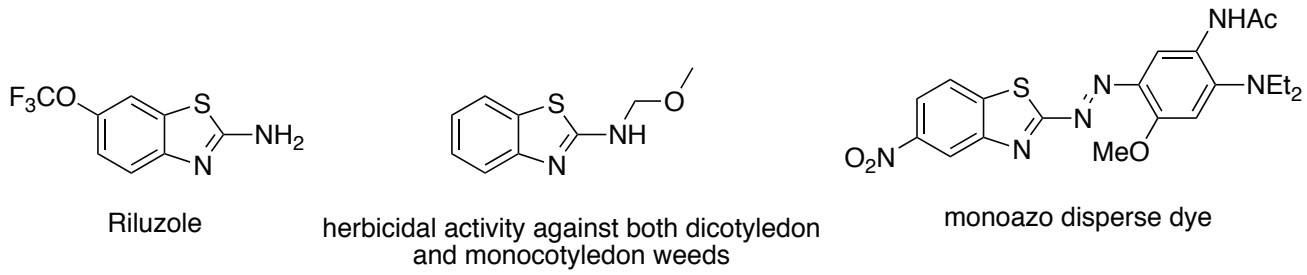


Figure 1. Benzothiazoles

On the other hand, many heterocycles that contain selenium, which, like sulfur, is a group 16 element, also exhibit biological activities. One example is Ebselen,[3] which acts as an antioxidant in peroxynitrite reduction,[3d] lipoxygenase inhibition,[3e] and glutathione peroxidase-like antioxidant[3f] (Figure 2).

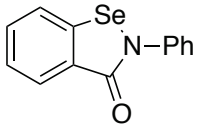
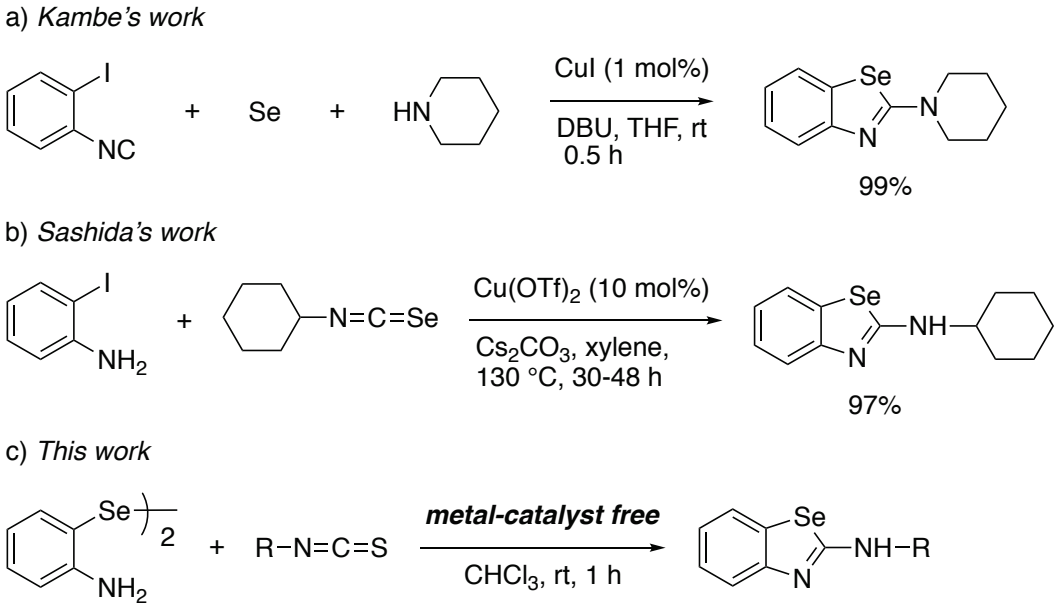


Figure 2. Ebselen

Benzoselenazole is also an attractive compound,[4] although there are few reports of its synthesis, particularly 2-amino-1,3-benzoselenazole synthesis, which is characterized by the cyclization of isonitrile or isoselenocyanate in the presence of a copper catalyst (Scheme 1).[5] Fujiwara, Kambe, and co-workers reported the synthesis of 1,3-benzoselenazole having a tertiary amino group at 2-position, which proceeds through a copper(I)-catalyzed cyclization reaction of 2-iodophenyl isocyanide with selenium and secondary amine, in excellent yield (Scheme 1a).[5a] Sashida and co-workers reported the preparation of 2-cyclohexylamino-1,3-benzoselenazole by a copper-catalyzed one-pot reaction of 2-iodoaniline and cyclohexyl isoselenocyanate (Scheme 1b).[5b] The copper catalyst was essential for the cyclization of selenazole into 2-amino-1,3-benzoselenazoles.



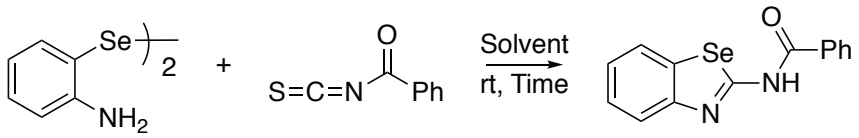
Scheme 1

Recently, metal-free processes have attracted attention as environmentally friendly and unique alternatives to metal-mediated cyclization reactions. Sun and co-workers reported the reaction of methyl

4-fluoro-3-aminobenzoate and some isoselenocyanates to generate corresponding 2-amino-1,3-benzoselenazole-5-carboxylates in moderate to good yields.[6] The substrate of this metal-free cyclization requires an electron-withdrawing group, such as a carbomethoxy group on the aromatic ring, because an S_NAr reaction involved. Herein, we report that the cyclization reaction of diaryldiselenide and various isothiocyanates in the absence of a transition metal catalyst gave 2-amino-1,3-benzoselenazoles (Scheme 1c). When acetyl isothiocyanate was used in this cyclization, the product could be easily deacetylated to generate 1,3-benzoselenazole with a free 2-amino group.

The reaction of bis(*o*-aminophenyl)diselenide (**1a**) and isothiocyanate **2a** was carried out in various solvents to generate *N*-2-(1,3-benzoselenazole)benzamide (**3a**). When such aprotic polar solvents as DMSO and DMF were used, the yields of **3a** were low (Table 1, Entries 1 and 2). It seems that a solvation to **2a** prevent to attack from **1a**. THF promoted the reaction and the product was obtained in 84% yield (Entry 3). Chloroform and benzene also gave good results (Entries 7 and 8). The reaction proceeded even in the absence of a solvent (Entry 9). We chose chloroform as the optimal solvent for this cyclization.

Table 1. Screening for solvent for preparation of benzoselenazole **3a**



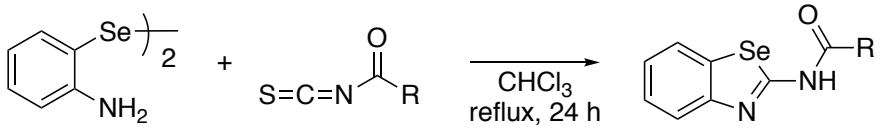
1a **2a** **3a**

Entry	Solvent	Time (h)	Yield (%)
1	DMSO	1	22
2	DMF	5	22
3	THF	1	84
4	Et_2O	1	56
5	toluene	3	51
6	CH_2Cl_2	4	61
7	$CHCl_3$	1	89
8	benzene	1	90
9	-	1	66

Next, we examined the effects of substituents of isothiocyanate **2**. The reactions of isothiocyanates **2a**–**h** and bis(*o*-aminophenyl)diselenide (**1a**) afforded benzoselenazoles **3** (Table 2). The reaction of *m*-methylbenzoyl isothiocyanate (**2b**) and **1a** gave **3b** in 90% yield, which almost paralleled the yield when benzoyl isothiocyanate **2a** was used (Entry 2). The use of aromatic acyl isothiocyanates gave corresponding 1,3-benzoselenazoles **3** in good yields. Interestingly, when alkylcarbonyl isothiocyanates,

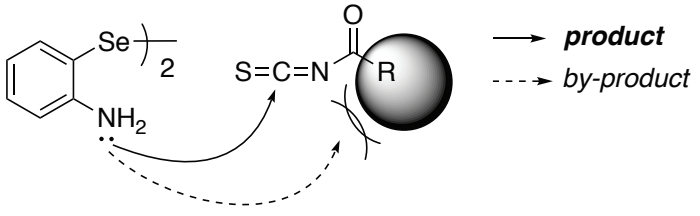
such as methyl, *n*-Pr, and *n*-pentyl, were used as substrates, corresponding benzoselenazoles were generated in 75%, 87%, and 99% yields, respectively (Entries 3–5). It is noteworthy that *i*-Pr and *t*-Bu carbonyl isothiocyanates also reacted with a diselenide despite the high steric hindrance (Entries 6 and 7). These results can be understood as follows. Bulky substituents, such as *n*-pentyl and *t*-Bu groups, would reduce the amounts of byproducts generated (Scheme 2). The first step of this reaction would be a nucleophilic addition of the diselenide amino group to acyl isothiocyanate. When a bulky substituent exists on the acyl group in **2**, the amino group of **1** would attack isothiocyanate carbon to generate a thiourea derivative (Scheme 2, solid arrow). However, when a less bulky group exists on the acyl group, the amino group would attack acyl carbon (Scheme 2, dashed arrow) to generate byproducts. Although byproducts which a diselenide attacks to the acyl moiety of an isothiocyanate was detected, they could not determine the structure from any NMR spectra. The results suggest that the nucleophilic addition of (aminophenyl)diselenide **1a** to isothiocyanates **2** is the rate-determining step of this cyclization.

Table 2. Synthesis of **3** from **1a** and **2** bearing various functional groups



1a **2** **3**

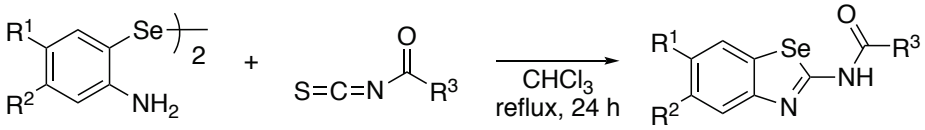
Entry	R	Product	Yield (%)
1	Ph (**2a**)	**3a**	89
2	*m*-MeC_6H_4 (**2b**)	**3b**	90
3	Me (**2c**)	**3c**	75
4	*n*-Pr (**2d**)	**3d**	87
5	*n*-Pent (**2e**)	**3e**	99
6	*i*-Pr (**2f**)	**3f**	76
7	*t*-Bu (**2g**)	**3g**	90
8	OEt (**2h**)	**3h**	74



Scheme 2

The substituents of diselenide **1** had no effects on this reaction (Table 3). When benzoyl isothiocyanate **2a** was used in the cyclization reaction with diselenides **1a**–**f**, which have electron-donating groups as well as electron-withdrawing groups, benzoselenazoles **3** were produced in good to excellent yields (Entries 1–6). On the other hand, except the case of **3c**, acetyl isothiocyanate (**2c**) generated **3** in low yields (Entries 7–11). It seems that a formation of byproducts cannot be ignored. The results suggest that the substituents of bis(*o*-aminodiphenyl)diselenide (**1**) have minimal influence on the cyclization into 1,3-benzoselenazoles.

Table 3. Synthesis of **3** from **2** and **1** bearing various functional groups



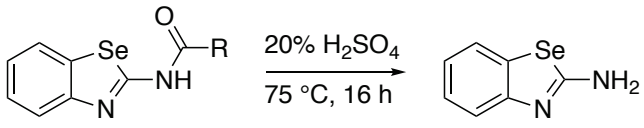
Entry	R^1, R^2(**1**)	R^3(**2**)	Product	Yield (%)
1	R^1=R^2=H(**1a**)	Ph(**2a**)	**3a**	89
2	R^1=H, R^2=Me(**1b**)	Ph(**2a**)	**3i**	73
3	R^1=H, R^2=OMe(**1c**)	Ph(**2a**)	**3j**	91
4	R^1=H, R^2=OEt(**1d**)	Ph(**2a**)	**3k**	99
5	R^1=H, R^2=Cl(**1e**)	Ph(**2a**)	**3l**	84
6	R^1=Cl, R^2=H(**1f**)	Ph(**2a**)	**3m**	89
7	R^1=R^2=H(**1a**)	Me(**2c**)	**3c**	75
8	R^1=H, R^2=Me(**1b**)	Me(**2c**)	**3n**	29
9	R^1=H, R^2=OMe(**1c**)	Me(**2c**)	**3o**	42
10	R^1=H, R^2=Cl(**1e**)	Me(**2c**)	**3p**	31
11	R^1=Cl, R^2=H(**1f**)	Me(**2c**)	**3q**	31

To obtain 1,3-benzoselenazoles with a free amino group at 2-position, we investigated the hydrolysis of **3**. Benzamide **3a** was treated with dilute sulfuric acid. However, no hydrolysis products were obtained in the conditions (Table 4, Entry 1). Then, aliphatic amides were treated with dilute sulfuric acid. The hydrolysis of acetamide **3b** proceeded smoothly to give 2-amino-1,3-benzoselenazole **4** in 80% yield (Entry 2). In contrast to the above results, the hydrolysis of amides with larger alkyl groups proceeded very slowly (Entries 3 and 4). It appears that the hydrolysis was affected by the solubility of the substrate. Since water was used as a solvent, it seems that increase of hydrophobicity and/or steric hinderance prevent the hydrolysis.

A plausible mechanism is shown in Scheme 3. The nucleophilic addition of **1** to **2** would generate a thiourea intermediate. The selenium atom of diselenide would attack the carbon of thiourea to induce

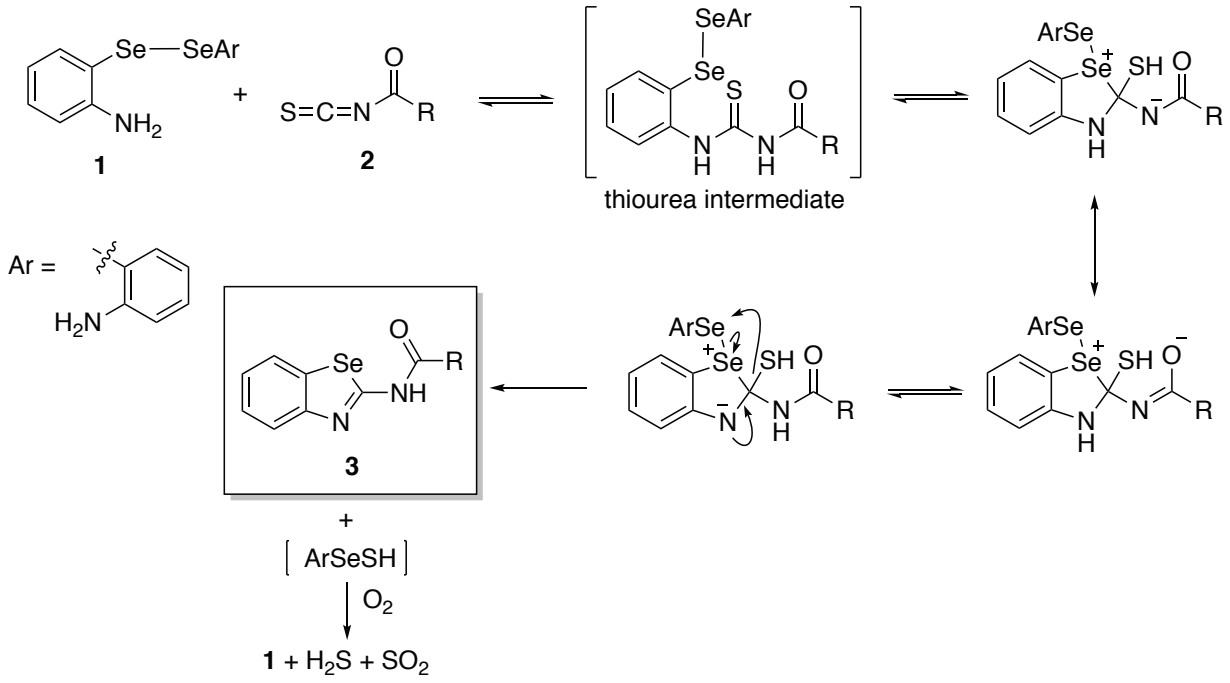
cyclization. After proton transfer, thiolate anion would be eliminated from the cyclic intermediate to attack another selenium atom to furnish **3** along with arylselenyl sulfide (ArSeSH), which would be oxidized to diselenide **1**, hydrogen sulfide, and sulfur dioxide. H_2S was detected as a white precipitate by the addition of silver nitrate solution. Arylselenyl sulfide plays an important role in redox biology and hydrogen sulfide continues to generate significant interest as an important biomolecule due to its role as a ubiquitous signaling molecule in diverse biological systems and processes.[7]

Table 4. Hydrolysis of **3** under acidic condition



3 **4**

Entry	R (**3**)	Yield (%)	Recovery (%)
1	Ph(**3a**)	0	99
2	Me(**3b**)	80	3
3	*n*-Pr(**3c**)	20	64
4	*n*-Pent(**3d**)	7	64
5	*i*-Pr(**3e**)	24	63
6	*t*-Bu(**3f**)	0	93



Scheme 3

The reaction of bis(*o*-aminophenyl)diselenide and acyl isothiocyanate in the absence of a transition metal catalyst gave 2-amino-1,3-benzoselenazole. Bulky acyl isothiocyanates provided the corresponding benzoselenazoles in good yields because the amounts of byproducts generated were reduced. It is important to note that arylselenyl sulfide and hydrogen sulfide, which are crucial biomolecules, have evolved from this cyclization. We are investigating the detailed reaction mechanisms.

SUPPORTING INFORMATION

Supplementary data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26264/101/2.

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