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One-pot copper-catalyzed tandem addition–cyclization of 2-iodoanilines with isoselenocyanates for the practical preparation of 2-aminobenzoselenazoles ☆

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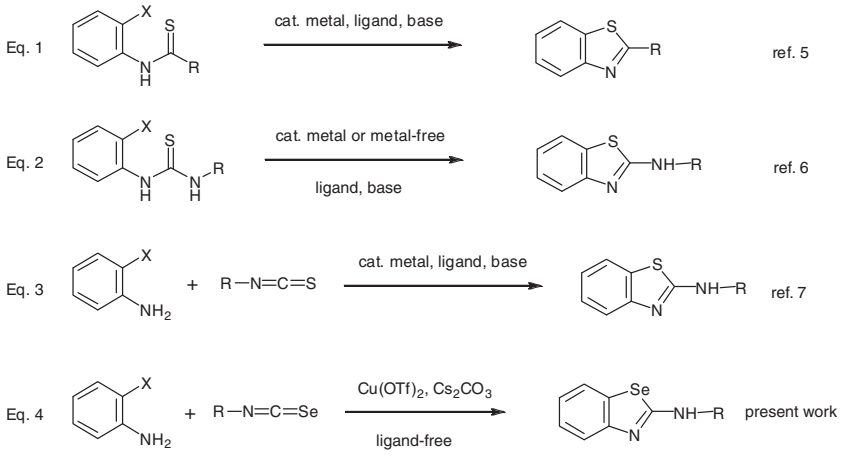
ABSTRACT

A convenient and successful one-pot preparation of the 2-aminobenzoselenazoles via the phenylselenoureas has been accomplished by the copper-catalyzed ligand-free reaction of the 2-iodoanilines and isoselenocyanates; the intermediate, selenoureas, were isolated, and quantitatively transformed into the selenazaoles.

Benzoheteroazoles are significant and important ring systems not only because of their attractive chemical properties and high reactivities but also of their wide biological activities. In particular, the synthesis of the 2-substituted benzimidazoles,[2] benzoxazoles,[3] and benzothiazoles[4] has attracted considerable interest. For the construction of the 2-substituted benzothiazoles, new methods include the transition metal-catalyzed or metal-free cyclization of 2-halophenylthioamides (Eq. 1 in Scheme 1)[5] and 2-halobenzothioureas (Eq. 2),[6] which are often generated from isocyanate derivatives.

One of the most important and convenient approach is the tandem reaction of the 2-haloanilines with the isothiocyanates via an intramolecular C–S bond formation requiring a ligand in most cases (Eq. 3).[7]

On the other hand, the similar reaction of the selenoanalogues, isoselenocyanates, with aniline derivatives still remains to be examined for the synthesis of the 2-substituted benzoselenazoles. It is worth noting that the treatment of the *o*-phenylenediamines with isoselenocyanates resulted in deselenacyclization to give the 2-aminobenzimidazoles,[8] not the selenium-containing heterocy-



Scheme 1.

☆ See Ref. 1.

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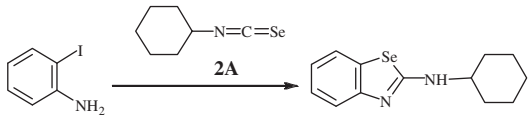
cles. There are only a few reports[9,10] on the preparation of the 2-substituted benzoselenazoles and related compounds, and their chemistry still remains unclean. The copper(I)-catalyzed reaction of 2-halophenyl isocyanides with selenium and heteroatom nucleophiles for the preparation of the 1,3-benzoselenazoles having a heteroatom substituent (NRR′, OR and SR) at the 2-position was disclosed by Kambe and co-workers in 2007.[9] Heimgartner and co-workers reported the synthesis of 2-aminoselenazolo[5,4-*b*]pyridines[10a] via the non-catalyzed reaction of 3-amino-2-chloropyridine with aryl isoselenocyanates in refluxing 2-propanol. Similarly, the 1*H*-1,3,6-triazaacenthrylene derivatives[10b] were also obtained from the pyrrolo[3,2-*c*]quinolines and isoselenocyanates in boiling pyridine.

Isoselenocyanates[11] are powerful synthetic precursors for the preparation of selenium-containing heterocycles because they are easy to prepare and store, and are safe to handle. Thus, there are many reports concerning the synthesis of selenium-containing heterocycles using isoselenocyanates. Very recently, we have also focused on the synthesis of the 1,3-benzoselenazines,[12] which are six-membered heterocycles containing nitrogen and selenium atoms; the synthetic method involves the intramolecular cyclization of the selenols, which used isoselenocyanates as the selenium source, into a triple bond.[13,14] In this Letter, the simple preparation of the benzoselanazoles by the copper-catalyzed one-pot reaction of 2-iodoanilines and isoselenocyanates is described.

A preliminary survey to optimize the reaction conditions was first carried out as shown in Table 1. The heating of 2-iodoaniline **1a** with 1.1 equiv of cyclohexyl isoselenocyanate **2A**, the secondary aliphatic isoselenocyanate, in xylene at 130 °C for 36 h resulted in decomposition that produced a complex mixture; the starting material **1a** was recovered in 17% yield (entry 1). When **1a** was similarly heated with **2A** in polar solvents, such as DMF, DMSO, and pyridine, the expected 2-aminobenzoselenazol **3Aa** was produced in 28%, 31%, and 16% yields, respectively; and a small amount of the starting material was recovered (entries 2–4). The reaction occurs under copper catalytic conditions (entries 5 and 7–13). Both copper iodide and copper(II) triflate were equally effective (entries 7 and 13). The addition of Cs_2CO_3 as a base afforded a good result, no selenazole **3Aa** was obtained by the addition of K_2CO_3 or Na_2CO_3 (entries 14–16). Finally, the combination of copper(II) triflate and Cs_2CO_3 in xylene was found to be the best condition for this tandem addition–cyclization reaction for the preparation of 2-aminobenzoselanazole **3Aa** (entry 17 vs 5–7, 14, and 18).[15] For this tandem addition–cyclization reaction, the $PdCl_2(Ph_3P)_2$ was not very effective (entry 19). Neither 2-bromoaniline nor 2-chloroaniline, which is superior in costs and synthetic easiness of substrates, gives **3Aa** under the same conditions; the starting anilines could not be recovered.

Table 1
Reaction of 2-iodoaniline **1a** with cyclohexyl isoselenocyanate **2A**[a]



1a **3Aa**

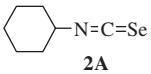
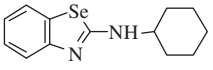
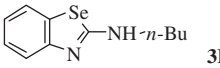
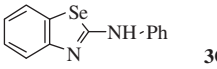
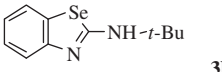
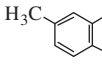
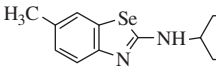
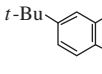
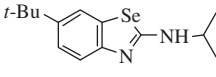
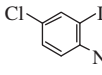
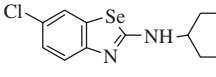
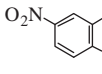
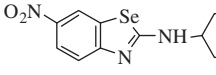
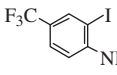
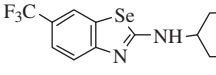
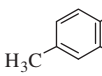
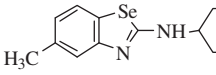
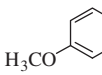
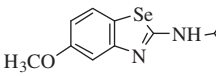
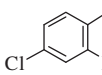
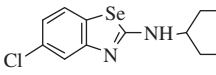
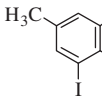
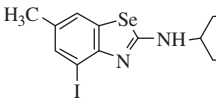
Entry	Solvent	Catalyst	Base	**3Aa**[b] (%)	Recovery[b] (%)
1	Xylene	None	None	0	17
2	DMF	None	None	28	8
3	DMSO	None	None	31	19
4	Pyridine	None	None	16	6
5	DMSO	$Cu(OTf)_2$	None	43	43
6	DMSO	None	Cs_2CO_3	10	52
7	Xylene	$Cu(OTf)_2$	None	48	6
8	Xylene	$CuBr_2$	None	19	0
9	Xylene	CuO	None	23	0
10	Xylene	$Cu(OAc)_2$	None	37	2
11	Xylene	CuCl	None	19	2
12	Xylene	CuBr	None	14	1
13	Xylene	CuI	None	49	0
14	Xylene	None	Cs_2CO_3	56	34
15	Xylene	None	K_2CO_3	0	3
16	Xylene	None	Na_2CO_3	0	5
17	**Xylene**	**$Cu(OTf)_2$**	**Cs_2CO_3**	**97**	**0**
18	Xylene	CuI	Cs_2CO_3	45	12
19	Xylene	$PdCl_2(Ph_3P)_2$	Cs_2CO_3	0	8

[a] Standard reaction conditions: **1a** (1 mmol), **2A** (1.1 mmol), catalyst (10 mol %), base (1.25 mmol), solvent (2.5 mL), 130 °C, 30–48 h.
[b] Isolated yield.

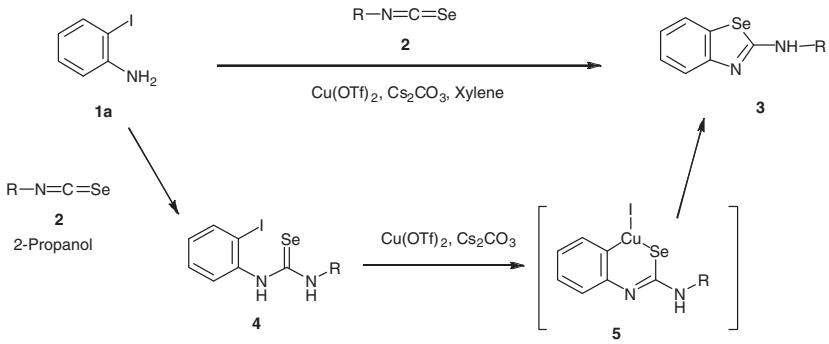
Next, the extension of this tandem addition–cyclization of 2-iodoanilines having various functional groups involving an electron-withdrawing and electron-donating group at the C-4 or C-5 position with some isoselenocyanates was carried out and the results are summarized in Table 2. 2-Iodoaniline **1a** reacted with the primary aliphatic isoselenocyanate, *n*-butyl isoselenocyanate **2B**, to give the corresponding benzoselenazole **3Ba** in 57% yield as the sole product (entry 2). The aromatic isoselenocyanate, phenyl isoselenocyanate **2C**, was also reactive enough to afford the corresponding selenazole **3Ca** in 77% yield (entry 3). However, replacing the isoselenocyanate by *tert*-butyl isoselenocyanate **2D** gave a complex mixture involving the slight yield of the selenazole **3Da**; the starting 2-iodoaniline **1a** was recovered in 55% yield because of the gradual decomposition of the isoselenocyanate **2D** under the optimized conditions (entry 4). The lower reactivity of *tert*-butyl isoselenocyanate **2D** may be due to the steric hindrance by the bulky tertiary butyl group. Thus, using the above mentioned optimized reaction conditions, we initiated our investigation into the scope of the reaction of various substituted 2-iodoanilines. The reaction of the 4-methyl- **1b** and 4-*tert*-butyl-2-iodoanilines **1c** having an electron-donating group at the C-4 position with cyclohexyl isoselenocyanate **2A** is well tolerated and provided the corresponding selenazoles **3Ab** and **3Ac** in isolated high yields (entries 5 and 6). 6-Chloroselenazole **3Ad** was also synthesized from 4-chloro-2-iodoaniline **1d** and isoselenocyanate **2A** in 87% yield (entry 7). On the contrary, when the tandem addition–cyclization of the 2-iodoanilines **1** having an electron-withdrawing group at the C-4 position, such as 4-nitro- **1e** and 4-trifluoromethyl-2-iodoaniline **1f** was carried out with **2A**, the corresponding selenazoles **3Ae** and **3Af** were obtained in 63% and 50% yields, respectively (entries 8 and 9). The decrease in the yields of the products **3Ae** and **3Af** may be explained by the lower reactivity due to the substitution of the electron-withdrawing group through the first step addition in this tandem reaction. Furthermore, the 5-substituted 2-iodoanilines were also treated with isoselenocyanate **2A** to produce the expected 5-functionalized selenazoles in moderate to good yields (entries 10–12). In addition, 2,6-diiodo-4-methylaniline **1j** reacted with isoselenocyanate **2A** to afford the selenazole **3Aj** in 62% yield (entry 13).

A possible mechanism for the formation of 2-aminobenzoselenazole **3** from 2-iodoaniline **1** with isoselenacyanate **2** is shown in Scheme 2. The successful copper-catalyzed intramolecular cyclization of the initial adduct, phenylselenourea **4** proceeded via the metalacycle **5** to give the selenazole **2**. Evidence for the generation of the phenylselenourea **4** could be confirmed by the isolation of **4Aa**. The reaction of 2-iodoaniline **1a** with isoselenocyanate **2A** gave the 2-aminobenzoselanazole **3Aa** in 97% yield (Table 1, entry 17). However, **3Aa** was not produced from either 2-bromoaniline or 2-chloroaniline under the same conditions; the starting anilines could not be recovered. This fact clearly indicated that the first step addition of the 2-haloaniline with the isoselenocyanate proceeded to give the adduct. After careful examination, phenylselenourea **4Aa** was isolated, which was produced by the reaction of **1a** with

Table 2
2-Aminobenzoselenazoles **3**

Entry	Anilines	Isoelenocyanate	Product	Yield[a] (%)
1	 **1a**	 **2A**	 **3Aa**	97
2	**1a**	*n*-Bu-N=C=Se **2B**	 **3Ba**	57
3	**1a**	Ph-N=C=Se **2C**	 **3Ca**	77
4	**1a**	*t*-Bu-N=C=Se **2D**	 **3Da**	3
5	 **1b**	**2A**	 **3Ab**	90
6	 **1c**	**2A**	 **3Ac**	91
7	 **1d**	**2A**	 **3Ad**	87
8	 **1e**	**2A**	 **3Ae**	63
9	 **1f**	**2A**	 **3Af**	50
10	 **1g**	**2A**	 **3Ag**	83
11	 **1h**	**2A**	 **3Ah**	78
12	 **1i**	**2A**	 **3Ai**	93
13	 **1j**	**2A**	 **3Aj**	62

[a] Isolated yield.



Scheme 2.

2A in refluxing 2-propanol in almost quantitative yield. The treatment of the adduct **4Aa** with copper(II) triflate and Cs_2CO_3 in xylene at 130 °C, which was the standard cyclization conditions, gave the selenazole **3Aa** in excellent yield. Compound **4Aa** was stably obtained and could be recrystallized, but decomposed during purification by silica gel chromatography. The reaction of 2-bromoaniline and 2-chloroaniline with isoselenocyanate in refluxing 2-propanol also gave the corresponding phenylselenou-

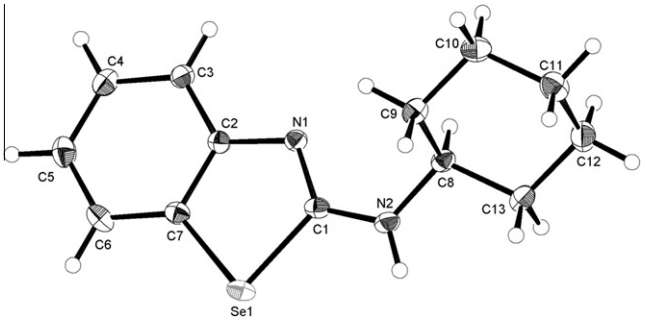


Figure 1. ORTEP drawing of **3Aa** with thermal ellipsoid plot (50% probability). Selected bond lengths (Å) and angles (°); Se1–C1 1.918(2), Se1–C7 1.887(2), C1–N1 1.301(3), N1–C2 1.398(3), C2–C7 1.406(3), C1–Se1–C7 84.05(9), N1–C1–Se1 116.0(2), C1–N1–C2 112.4(2), N1–C2–C7 117.7(2), C2–C7–Se1 109.8(2).

reas, which were not converted into the desired selenazoles under the optimized conditions. Therefore, not only products but also starting anilines were not obtained by the reaction of 2-bromoaniline and 2-chloroaniline with isoselenocyanate .

The structures of these 2-aminobenzoselenazoles **3** were determined by their MS, ^{1}H, and ^{13}C NMR spectra and elemental analyses, and finally established by single-crystal X-ray studies using cyclohexyl derivative **3Aa** (Fig. 1).[16]

In summary, the one-pot copper-catalyzed ligand-free tandem addition–cyclization of the 2-iodoanilines with the isoselenocyanates for the practical synthesis of the 2-aminobenzoselenazoles via the C–Se bond formation of the 2-iodophenyl selenoureas smoothly occurred; the intermediates, selenoureas, could be isolated. A variety of 2-aminobenzoselenazoles were easily obtained in moderate to high yields.

Acknowledgments

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References and notes

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15. A typical experimental procedure for tandem addition–cyclization of 2-iodoaniline **1a** with isoselenocyanate **2A** is as follow: A mixture of 2-iodoaniline **1a** (219 mg, 1 mmol), cyclohexyl isoselenocyanate (208 mg, 1.1 mmol), $Cu(OTf)_2$ (0.1 mmol), and $CsCO_3$ (1.25 mmol) in dry xylene (2.5 mL) was heated at 130 °C for 30–48 h under argon atmosphere. The mixture was diluted with benzene (30 mL), and the organic layer was washed with water (20 mL × 2), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The obtained residue was purified by silica gel chromatography using $CHCl_3$–MeOH (100:3) as eluent to give pure 2-cyclohexylaminobenzoselenazole **3Aa**. Yield: 272 mg (97%). Colorless needles, mp 141–142 °C ($CHCl_3$–hexane). IR (KBr-tab): 3178 (NH), 1591 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.14–1.44, 1.57–1.66, 1.71–1.78, 2.07–2.14, 3.37–3.45 (5H, m, 1H, 2H, m, 2H, m, 1H, m, cyclohexyl-H), 6.11 (1H, br s, NH), 6.98, 7.26, 7.51, 7.60 (1H, dd, J = 7.8, 7.3 Hz, 1H, dd, J = 8.1, 7.3 Hz, 1H, d, J = 8.1 Hz, 1H, d, J = 7.8 Hz, Ph-H). ^{13}C NMR ($CDCl_3$) δ: 24.8 (t), 25.4 (t), 33.3 (t), 56.0 (d), 119.8 (d), 121.4 (d), 124.1 (d), 126.1 (d), 132.8 (s), 154.1 (s), 167.2 (s). EI-MS: m/z (%) = 280 (M^+, 52), 223 (8), 198 (100), 171 (13). EI-HRMS: m/z calcd for $C_{13}H_{16}N_2{}^{80}Se$ [M^+]: 280.0479; found: 280.0481.
16. Single crystals of **3Aa** were obtained from solutions of methanol/dichloromethane after slow evaporation of the solvent at room temperature. Diffraction data were collected on a Bruker Apex-II CCD diffractometer equipped with a graphite monochromated MoKα radiation source (λ = 0.71073 Å). The structures were solved by direct methods (SHELXS-97),[17] and refined by full-matrix least-square methods on F^2 for all reflections (SHELXL-97)[18] with all non-hydrogen atoms anisotropic and all hydrogen atoms isotropic. For **3Aa**, the structure analysis is based on 2926 observed reflections with $I > 2.00\sigma(I)$ and 150 variable parameters; purple needles, 196 K, trigonal, space group $R\bar{3}$, a = 23.670(4) Å, b = 23.670(4) Å, c = 11.9466(18) Å, V = 5796.5(2) Å^3, Z = 18, R = 0.0268, R_w = 0.0681, GOF = 1.118. CCDC 793875 for **3Aa** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.
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