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Cu-Catalyzed Efficient Synthetic Methodology for Ebselen and Related Se−N Heterocycles

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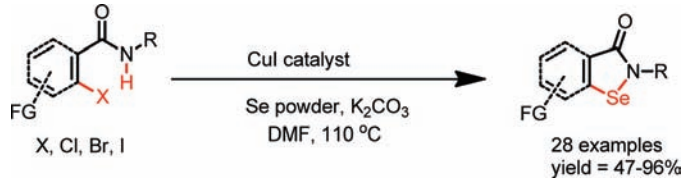
ABSTRACT



An efficient copper-catalyzed method for the synthesis of biologically important ebselen and related analogues containing a Se−N bond has been developed. This is the first report of a catalytic process of selenation and Se−N bond formation reaction. Copper-catalyzed reaction tolerates functional groups such as amides, hydroxyls, ethers, nitro, fluorides, and chlorides. The best results are obtained by using a combination of potassium carbonate as a base, iodo- or bromo-arylamide substrates, selenium powder, and copper iodide catalyst.

Ebselen (**1**, 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one) and related analogues comprising a Se−N bond have attracted considerable interest in biology and chemistry in view of their promising antioxidant function.[1−3] Indeed, ebselen is the first known selenium compound with minimal toxicity and is in clinical studies for the treatment of inflammatory diseases and strokes.[3b,4] Ebselen and its analogues have also been used as oxygen transfer catalysts for the synthesis of organic molecules.[5]

Despite the clear biological importance, the synthesis of selenazolones is challenging and mainly relies on two methods: *ortho*-lithiation of benzanilide[6] and a multistep route which depends on bis(*ortho*-benzoic acid) diselenide (Scheme 1, eqs 1 and 2).[7] Other synthetic methods for the synthesis of Se−N heterocycles have also been reported; however, most of them depend upon their respective diorgano diselenide multistep route or selenium reagents such as $SeBr_2$ and KSeCN.[8,9]

In spite of many reported methods on Se−N heterocycles, the construction of a Se−N bond is an intriguing step.

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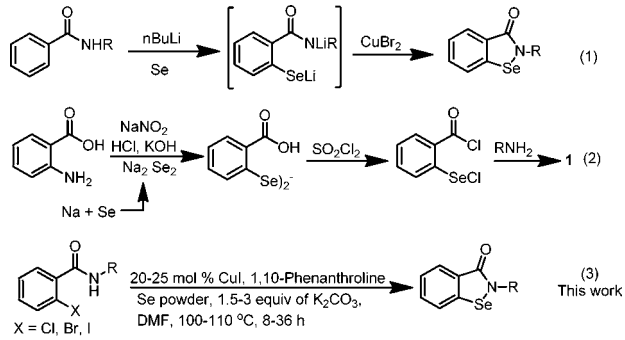
Scheme 1. Synthetic Routes to Ebselen and Related Selenazolones



Furthermore, to the best of our knowledge, there is no catalytic method available for the synthesis of ebselen and related selenazolones.

In recent times, transition-metal-catalyzed coupling has become an important method for the formation of aromatic carbon−heteroatom bonds. Among this class of reactions, Cu- and Pd-catalyzed syntheses of organosulfur and -selenium compounds have been explored.[10,11] Herein, for the first time, we report a general, efficient, and catalytic approach for the synthesis of biologically important Se−N heterocycles from halo-amides and selenium powder in the presence of a base (eq 3).

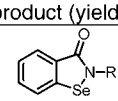
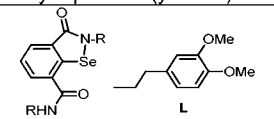
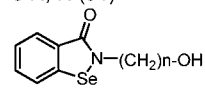
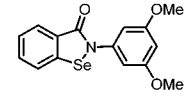
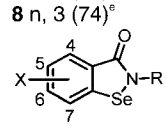
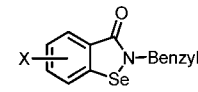
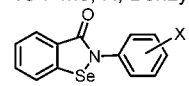
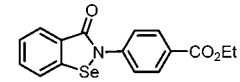
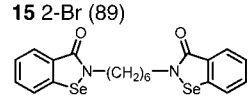
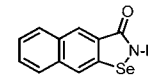
Reaction conditions for the Cu-catalyzed synthesis of Se−N heterocycles were optimized with 2-iodo-*N*-phenylbenzamide. After extensive screening, the high yield of product was obtained when iodo-amide was treated with 20 mol % of CuI and 1,10-phenanthroline and selenium powder in the presence of K_2CO_3 in DMF (eq 3, Table 1). The Cu-catalyzed reaction was applied to the synthesis of a series of Se−N heterocycles (**1**−**28**) which were obtained in moderate to excellent yields (Table 2). Ebselen **1** was obtained in 84% yield from 2-iodo-amide. On performing the same reaction at 74 mmol scale, the yield is comparable with 3 mmol (84 vs 80%, entry 1). Following the same strategy, *N*-alkyl, *N*-benzyl-substituted Se−N heterocycles (**2**−**5**) were synthesized in excellent yields. Heterocycles **1** and **2** were also obtained from respective bromo substrates in nearly the same yield, although, reaction time was longer than for the iodo substrates (see Supporting Information, pages S3−S5).

Table 1. Cu-Catalyzed Formation of **1**: Survey of Reaction Conditions[a]

entry	CuI/L, base	solvent	temp (°C)	time (h)	yield
1	CuI/L, K_2CO_3	THF	110	12	trace[b]
2	CuI/L, K_2CO_3	DMSO	110	12	none
3	CuI/L, K_2CO_3	DMF	110	8	84%
4	CuI/L, K_2CO_3	DMF	r.t.	24	trace[b]
5	CuI/L, Et_3N	DMF	110	24	40%[c]
6	CuI/L	DMF	110	12	None
7	K_2CO_3[d]	DMF	110	48	trace[b]

[a] 20 mol % of CuI/1,10-phenanthroline (L) and 1.5 equiv of base used unless otherwise indicated. [b] Monitored by TLC. [c] Isolated yield and 27% of substrate recovered. [d] 5 equiv of K_2CO_3 used.

Table 2. Cu-Catalyzed Synthesis of Se−N Heterocycles from Halo Aryl Amides by Following Equation 3

entry	product (yield %)[a]	entry	product (yield %)[a]
			
1	**1** R, Ph (84) (80)[b] (78)[c] (47)[d]		L
2	**2** R, Benzyl (94), (91)[c]	17	**17** R, Ph (96)[c,e]
3	**3** R, Me (92)	18	**18** R, Benzyl (95)[c,e]
4	**4** R, Cyclohexyl (91)	19	**19** R, Phenylethyl (87)[c,e]
5	**5** R, Phenylethyl (96)	20	**20** R, L (90)[c,e]
6	**6** R, H (91)[e]		
			
7	**7** n, 2 (71)[e]	21	**21** (89)
8	**8** n, 3 (74)[e]		
			
9	**9** 7-NO_2, R, Benzyl (87)[d]	22	**22** 6-Cl (88)
10	**10** 7-NO_2, R, Ph (77)[d]	23	**23** 5-F (87)[d]
11	**11** 6-NO_2, R, Benzyl(90)[d]	24	**24** 6-F (87)[d]
12	**12** 5-NO_2 R, Benzyl (83)[d]	25	**25** 5,6-di-F (85)[d]
13	**13** 7-Me, R, Benzyl (87)		
			
14	**14** 4-Br (82)[c]	26	**26** (82)
15	**15** 2-Br (89)		
			
16	**16** (57)	27	**27** R, Ph (79)
		28	**28** R, Benzyl (93)

[a] Isolated yield obtained from iodo-amide substrates using 20 mol % of CuI/L and 1.5 equiv of K_2CO_3 unless otherwise stated. [b] Yield at 74 mmol scale. [c] Yields obtained from Ar−Br substrates. [d] Yields obtained from Ar−Cl substrates. [e] 25 mol % of CuI/L, K_2CO_3 (3 equiv) used.

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Interestingly, 2-iodo-benzamide having an additional acidic proton is compatible with this reaction (entry 6). Similarly, halo aryl amides with unprotected aliphatic hydroxyl or an additional −C(O)NHR group coupled to form Se−N heterocycles (entries 7−8 and 17−20). Furthermore, activated chloro amides (entries 9−12 and 23−25) quantitatively undergo coupling reaction to form Se−N heterocycles. In an earlier reported method, depicting the synthesis of nitro-substituted ebselen **9** has proven to be difficult. The obtained yield is 17% by the reaction of 2-bromo-3-nitrobenzoic acid with MeSeH followed by subsequent treatment with bromine.[12] The present catalytic method is a single-pot reaction by which a series of nitro-substituted ebselen analogues (**9**−**12**) were synthesized in high yield (77−90%) from chloro substrates. After exploiting activated chloro substrates in Se−N coupling reaction, we attempted to use chloro substrates to synthesize ebselen **1** (entry 1). Indeed, the reaction gave ebselen; however, the reaction was sluggish, and **1** was obtained in 47% yield. Substrates with fluoro, chloro, bromo, ester, methoxy, and methyl functionality were amenable to the Cu-catalyzed reaction. It is noteworthy that the Se−N coupling reaction is invariant to the presence of electron-donating (entries 13 and 21) or -withdrawing (entries 9−12, 14, 15, and 22−25) substituents on both aromatic rings. Moreover, for the corresponding dibromo substrate bearing an *N*-(4-bromo)phenyl ring (entry 14), the Se−N coupling reaction occurred regioselectively to give heterocycles **14**.

Synthesis of bis Se−N heterocycle **16** bearing two ebselen moieties has proven to be problematic and often obtained a monomer when *ortho*-(chloroseleno)benzoyl chloride coupled with 1,6-diamino hexane (eq 2).[1d,13] Copper-catalyzed coupling was successfully extended to the construction of bis Se−N heterocycle **16**.

After obtaining results on benzene-based amides, we studied the generality of the Cu-catalyzed reaction for other aromatic substrates: naphthalene-, pyridine-, and thiophene-amides. As expected, iodo-naphthyl amides were converted into the corresponding heterocycles **27** and **28** by this catalytic reaction. However, efforts to synthesize pyridine- and thiophene-based Se−N heterocycles from easily accessible bromo substrates have been unsuccessful.

The structure of naphthyl Se−N heterocycle **28** was established by both spectroscopic and single-crystal X-ray diffraction techniques (Figure 1).[14]

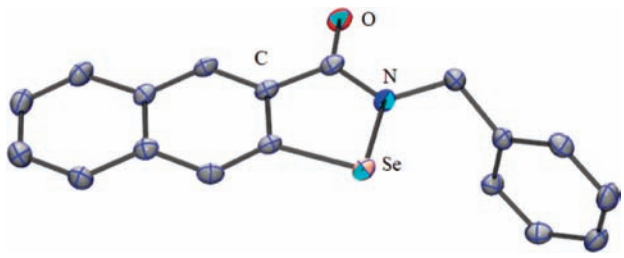
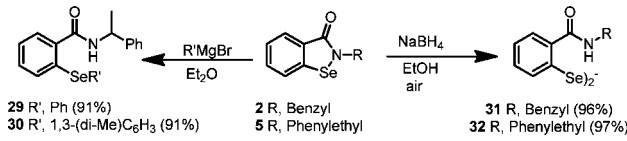


Figure 1. ORTEP view of **28** with 50% ellipsoidal probability. H-atoms are omitted for clarity.

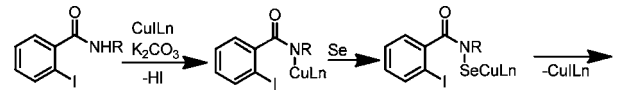
Scheme 2. Conversion of Se−N Heterocycles to Unsymmetrical Aryl Selenides and Diaryl Diselenides



As depicted in Scheme 2, we studied the utility of Se−N heterocycles for the preparation of synthetically important unsymmetrical diaryl selenides and diaryl diselenides. Addition of Grignard reagent[15] to **5** furnished **29** and **30**, and similarly, reduction and oxidation of **2** and **5** by $NaBH_4$ and air, respectively, afforded diselenides **31** and **32** quantitatively.

To understand the catalytic cycle of Se−N coupling, the following reactions were investigated: (a) in the absence of K_2CO_3; (b) in the absence of CuI/1,10-phenanthroline. None of the reactions yielded Se−N heterocycle **1**. Also 100 mol % of CuI/ligand in the absence of K_2CO_3 failed to produce **1** under optimized conditions. However, when the reaction was heated longer (48 h) in the presence of excess K_2CO_3, traces of **1** were observed. In light of these experiments and reported copper−amide complexes,[16] it is reasonable to assume that this is a base-promoted reaction in which Cu−amide complex formation would take place followed by insertion of selenium into the Cu−N bond and finally reductive elimination of CuILn leading to the formation of the Se−C bond (Scheme 3).

Scheme 3. Proposed Mechanism for the Se−N Coupling Reaction



In summary, we have shown that a one-pot Cu-catalyzed reaction can be applied to synthesize a series of organo Se−N heterocycles from readily available halo-amides and selenium powder. Selenazolones with unprotected functional groups could also be obtained in one pot. Catalytic studies on Se−N

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(14) X-ray quality crystals of **28** were obtained from DCM:hexane (7:3) solvent mixtures. Crystal data: $C_{18}H_{13}NOSe$, MW = 338.25, CCDC Number: 769448, a = 12.3938(3) Å, b = 18.8824(5) Å, c = 5.9739(2) Å, V = 1398.04(1) Å^3, Orthorhombic, $Pna2_1$, λ = 0.71073, Mo Kα, Z = 4, μ = 2.683, F(000) 679.9; $\theta_{min,max}$ = 2.71, 24.99. No. of unique refls/parameters: 2459/190; R_obs, wR_obs = 0.0242, 0.0480; $\Delta\rho_{max,min}$ 0.230, −0.322, GoF 0.887. Selected bond lengths and angles: C−Se, 1.893(3) Å; Se−N, 1.881(2) Å; C═O, 1.237(3) Å; C(5)−N, 1.356(3) Å; N−Se−C(7), 85.4 (9)°.

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heterocycles and characterization of intermediates involved in the Se−N coupling reaction are currently in progress in our laboratory.

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Supporting Information Available: Experimental details, characterization data (NMR and mass) for selected compounds, and CIF file for **28** (CCDC No. 769488). This material is available free of charge via the Internet at http://pubs.acs.org.

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