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Aerobic Radical-Cascade Cycloaddition of Isocyanides, Selenium and Imidamides: Facile Access to 1,2,4-Selenadiazoles under Metal-Free Conditions

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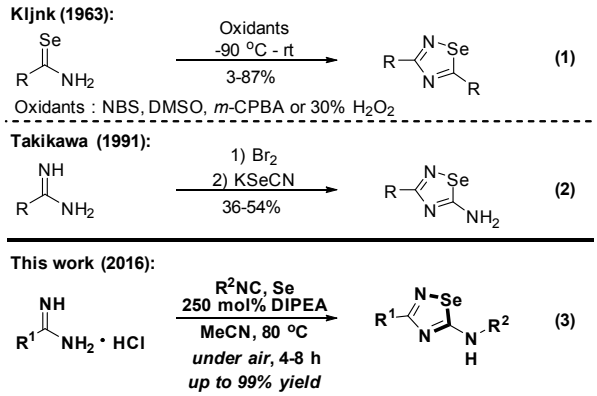
A novel and facile metal-free method for the green synthesis of 1,2,4-selenadiazol-5-amine derivatives through the aerobic radical-cascade multi-component reactions of isocyanides, selenium powder and imidamides is reported here. O_2 in the air was employed as the green oxidant to achieve the cycloaddition with the generation of H_2O as the sole by-product. It also features good functional group compatibility and broad substrate scope. In addition, this method was successfully applied to the functionalization of biologically active molecules.

Organoselenium compounds have shown great diversity and wide applications in synthetic organic chemistry.[1] What's more, they have been recognized as active reagents with potent biological and medical activities.[2-5] 1,2,4-Selenadiazoles, analogue of 1,2,4-thiadiazoles,[6] are potential important scaffolds for the construction of bioactive compounds. However, the reported approaches to the synthesis of 1,2,4-selenadiazoles are still rare.[7] Selenocarboxamides were employed as starting materials in most of the groundbreaking explorations. In existing methods, stoichiometric amounts of oxidants[7a-e], palladium(II) salt[7f] or toxic liquid bromine[7g-h] should be used (Scheme 1, eq.1 and 2). As a result, the yields of products were low and the substrate scope was limited, besides, laborious manipulation was required. Noble transition metal catalysts or various environmental unfriendly additives are required in most of the methods. Therefore, developing a novel, facile and green approach for the synthesis of 1,2,4-selenadiazoles is still highly desirable.



Scheme 1. Synthetic approaches to 1,2,4-selenadiazoles.

Diazenedicarboxylic acid (DEAD),[8] Oxone,[9] hypervalent iodine compounds[10], copper(II) salt[11] and element sulphur[12] were employed to promote or catalyse the oxidative coupling of the N-S bond for the synthesis of 1,2,4-thiadiazoles. In comparison, selenium shows greater metallic character than sulphur and thus selenium is more susceptible to oxidation. In view of this fact, we envisage that the synthesis of 1,2,4-selenadiazole compounds could be achieved by utilization of milder oxidizing agent. Oxygen is an ideal oxidant, usually, its reduction product is water instead of organic or metal wastes, thus it can be called 'green oxidant'. So, applying O_2 in the oxidative coupling process of N-Se bond is environmental friendly.

Retrosynthetic analysis of 1,2,4-selenadiazol-5-amines show that the assembly of 1,2,4-selenadiazol-5-amines can be accomplished by using imidamides and isoselenocyanates (Scheme 2). Imidamides are commercially available from a wide variety of sources, or they can be easily synthesized from nitriles[13] or esters.[14] Isoselenocyanates could be obtained *in situ* by mixing selenium powder with isocyanides.[15] Besides, isocyanides are easy to prepare in large amounts with great diversity.[16,17] In addition, selenium powder is an ideal and

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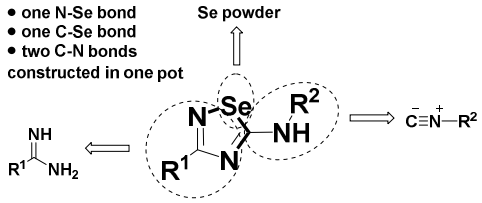
direct source to construct organoselenium compounds. In contrast with inorganic selenium compounds (SeO_2, $SeCl_2$, Na_2SeO_3, Na_2SeO_4, KSeCN, etc.), which are highly toxic and unstable, the selenium powder is hypotoxic and easy to handle. The ready availability and diversity of the three chunks also ensure the broad substrate scope of 1,2,4-selenadiazol-5-amines. As part of our interests in isocyanide chemistry,[18,19] herein, we demonstrated a user-friendly and environmentally-friendly strategy for preparing 1,2,4-selenadiazol-5-amines through the aerobic radical-cascade multi-component reactions of isocyanides, selenium powder and imidamides under metal-free conditions (Scheme 1, eq. 3). The starting materials are readily available and easy to handle, exploiting oxygen as the green oxidant with the generation of water as sole by-product.

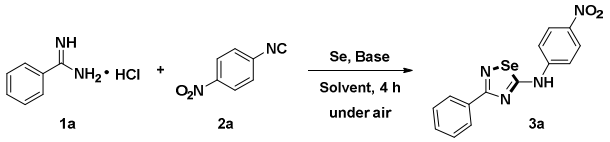


Scheme 2. Retrosynthetic analysis of 1,2,4-selenadiazol-5-amines.

Results and discussion

We initiated the studies by the reaction of benzamidine hydrochloride (**1a**) with *p*-nitrophenyl isocyanide (**2a**) in the presence of selenium powder. It was found that *N*, *N*-diisopropylethylamine (DIPEA) served as an efficient base (Table 1, entry 2), affording the desired product **3a** in 73% yield. Other organic bases (Table 1, entries 1, 3-6) or inorganic bases (Table 1, entries 7-10) were also investigated, but lower yields were obtained. Further screening of the reaction temperatures and solvents showed that conducting the reaction in MeCN at 80 °C gave better results (Table 1, entry 14). Finally, the highest yield (92%) was obtained by increasing the amount of **2a** and selenium powder to 1.5 equivalents and the amount of DIPEA to 2.5 equivalents (Table 1, entry 17).

Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	T [°C]	Yield [%][b]
1	Et_3N	DMSO	50	72
2	DIPEA	DMSO	50	73
3	DABCO	DMSO	50	70
4	pyridine	DMSO	50	46
5	TMG	DMSO	50	17
6	DBU	DMSO	50	trace
7	K_2CO_3	DMSO	50	52
8	Na_2CO_3	DMSO	50	44
9	Cs_2CO_3	DMSO	50	57
10	K_3PO_4	DMSO	50	38
11	DIPEA	DMSO	80	75
12	DIPEA	DMA	80	73
13	DIPEA	DMF	80	82
14	DIPEA	MeCN	80	85
15	DIPEA	THF	80	71
16	DIPEA	Dioxane	80	72
17	DIPEA	MeCN	80	92[c]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Se (0.24 mmol), base (0.4 mmol), solvent (2 mL), under air. [b]Yields were determined by LC analysis using biphenyl as an internal standard. [c]**1a** (0.2 mmol), **2a** (0.3 mmol), selenium (0.3 mmol) and DIPEA (0.5 mmol).

With the optimized conditions in hand, we explored the substrate scope of various isocyanides **2**. To our delight, an array of aromatic isocyanides could participate in this three-component reaction to give the 1,2,4-selenadiazol-5-amines in 65-95% yields (Table 2, top). Electron-withdrawing groups, such as nitro (**3a**, **3b**), trifluoromethyl (**3c**), and cyano (**3d**) moieties, are compatible with the reaction. Substrates bearing electron-donating groups, such as methoxy (**3e**, **3f**) and methyl (**3g**) gave better results, leading to the expected products in 95%, 95% and 87% yields, respectively. In addition, the iodo group (**3h**) was tolerated under current conditions. Moderate to good yields could also be obtained when aliphatic isocyanides were employed (Table 2, middle). Tertiary isocyanides were proven to be suitable candidates for the one-pot reaction, giving rise to the desired selenadiazoles (**3i**, **3j**, **3k**), albeit in moderate yields. In contrast, *N*-cyclohexyl substituted isocyanide worked with improved efficiency to deliver the product **3l** in excellent yield. Besides, reactions involving benzyl isocyanides and ethyl isocyanoacetate produced **3n** and **3o** in 80% and 76% yields, respectively. Disappointedly, we could not obtain products **3m** and **3p** under the optimized conditions. Next, we investigated the substrate scope with respect to the imidamides (Table 2, bottom). A variety of aromatic imidamides are tolerated, with the generation of selenadiazoles in high yields. Both substrates bearing electron-donating **(3q**, **3r)** and electron-withdrawing groups **(3s**, **3u**, **3v**, **3w**, **3x**) could react smoothly. In addition, the structure of **3u** was unambiguously determined by X-ray crystallography (see SI for details).[20] Fortunately, hydroxyl

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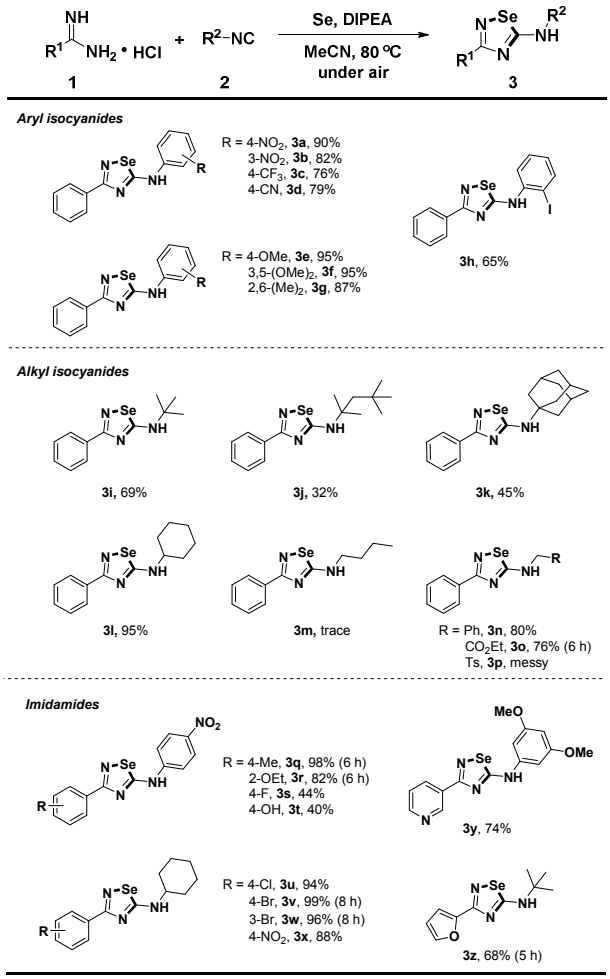
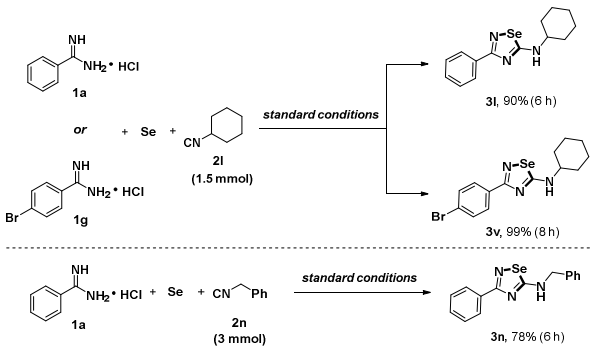
group was also tolerated, giving **3t** in 40% yield. Moreover, heterocycles, such as pyridine and furan, were compatible with the mild reaction conditions as well, leading to **3y** and **3z** in 74% and 68% yields, respectively.

Table 2 Substrate scope of reaction[a,b]



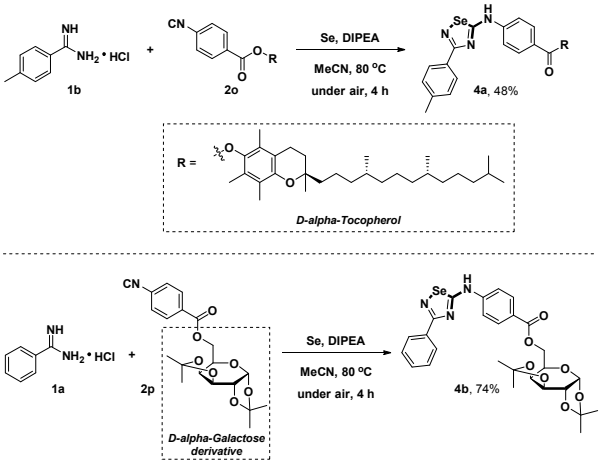
[a]Reaction conditions: 1 (0.3 mmol), 2 (0.45 mmol), Se (0.45 mmol), DIPEA (0.75 mmol), MeCN (3 mL), 80 °C, under air, 4 h. [b]Isolated yields.



Scheme 3. Scale-up synthesis of 1,2,4-selenadiazole-5-amines.

In order to show the efficiency of our method, we explored the scale-up reactions of **1a** or **1g** with cyclohexyl isocyanide **2l** under the standard reaction conditions. Gratifyingly, the desired products **3l** and **3v** were obtained in 90% and 99% yields, respectively. When the amount of **2n** was enlarged to 3 mmol, we were pleased to find that **3n** could be obtained in 78% yield after 6 hours, without compromising reaction efficiency (Scheme 3). These results suggested that this method had potential for industrial production.

To illustrate the importance of the synthetic method, we applied it to the late-stage modification of the bioactive natural compound and saccharide compound (Scheme 4). When we performed the reaction of tocopherol derivative **2o** with **1b** under standard conditions, we were able to obtain 48% yield of the desired product **4a**. In addition, when galactose derivative **2p** was employed under standard reaction conditions, we could isolate **4b** in 74% yield, providing a new method for the synthesis of novel biologically and pharmaceutically active compounds.



Scheme 4. Late-stage functionalization of biologically active molecules.

To gain a deep insight into the reaction mechanism, we conducted several controlled experiments. Firstly, when radical scavengers TEMPO and BHT were added to the reaction mixture under standard conditions, **3l** could be produced in up to 87% yield. Although decrease of *ca.* 10% yield was observed, the increase of equivalents of TEMPO had no significant impact on the outcomes (Scheme 5, eq. 4). The results of radical-inhibition experiments indicated that the reactions were prone to undergo a non-radical process, though we could not rule out the existence of radicals rigorously. TEMPO could act as not only a radical inhibitor, but also a radical initiator. It is known that two single electrons exist in the oxygen molecule, thus we proposed that oxygen might serve as an essential single-electron initiator in the transformation. As a result, the same reaction under argon was performed as well. As expected, the reaction could not occur at all. However, a 81% yield of **3l** could be isolated when additional TEMPO (1.5 equiv.) was employed (Scheme 5, eq. 5). We believed that the single-electron oxidant TEMPO could facilitate the radical-cascade cyclization reaction, which is also consistent with the radical-inhibition experiments.

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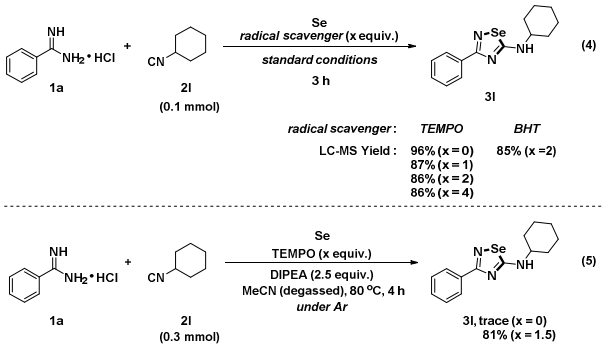
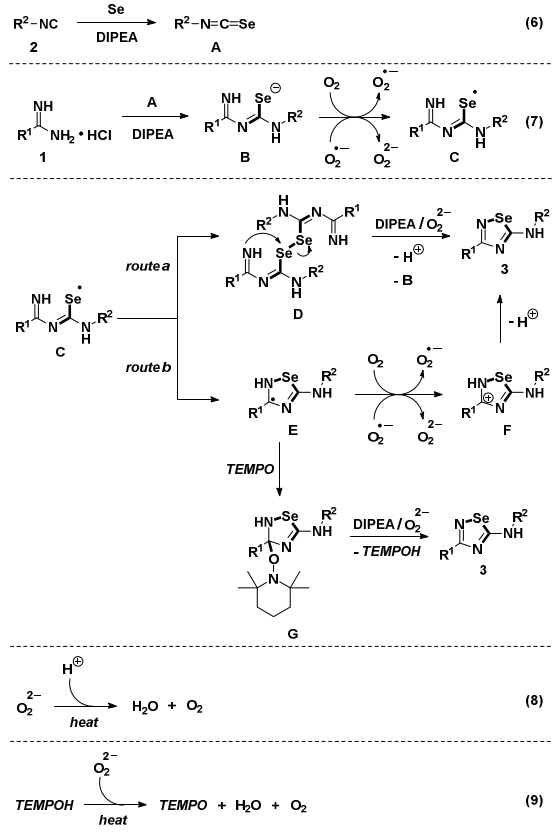


Scheme 5. Investigation of reaction mechanism.

Inspired by the above results, a SET (single electron transfer) process was proposed to elucidate reaction mechanism (Scheme 6). Firstly, the reaction of isocyanide **2** with selenium powder gives isoselenocyanate **A** under the action of DIPEA (Scheme 6, eq. 6). Next, **A** reacts with imidamide **1** to produce the intermediate **B**. Subsequently, **B** is oxidized by O_2 or superoxide anion radical to give selenium radical intermediate **C** (Scheme 6, eq. 7). We propose that **C** may undergo two possible pathways to generate the desired product **3**. In the first pathway, diselenide intermediate **D** is generated by homocoupling of **C**,[21] followed by deprotonation under the action of DIPEA or peroxide anion, to afford product **3** (Scheme 6, *route a*). An intramolecular cyclization of **C** is involved in the



Scheme 6. Plausible reaction mechanism.

second pathway for the formation of intermediate **E**, then **E** undergoes deprotonation under the influence of DIPEA or peroxide anion to yield **3** (Scheme 6, *route b*). We believe that TEMPO can trap intermediate **E** to generate **G**, which is unstable under the reaction conditions. As a result, a molecule of TEMPOH will be eliminated by DIPEA or peroxide anion to produce **3**, which explains the aforementioned results why TEMPO could not inhibit the reaction.[22] The peroxide anion and proton, which is formed in the reaction, will combine and thermally decompose to H_2O and O_2 (Scheme 6, eq. 8). In addition, TEMPO is regenerated from TEMPOH under the action of peroxide anion (Scheme 6, eq. 9).[23] At present, neither of the plausible reaction routes could be ruled out. More control experiments or theoretical calculation should be conducted to further gain insights into the reaction mechanism.

Conclusions

In summary, we have developed a practical method to synthesize 1,2,4-selenadiazole-5-amine derivatives in moderate to excellent yields by multicomponent reaction of isocyanides, selenium powder and imidamide compounds under metal-free conditions. The reaction proceeds under mild conditions with O_2 as green oxidant and no extra catalysts or oxidants are required. What's more, this method can be used for late-stage modification of biologically and pharmaceutically active molecules, which featured the reaction in the discovery and development of selenium-containing drugs. A detailed mechanistic study and further potential applications of this clean reaction in medicinal chemistry are currently undergoing in our laboratory.

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Aerobic Radical-Cascade Cycloaddition of Isocyanides, Selenium and Imidamides: Facile Access to 1,2,4-Selenadiazoles under Metal-Free Conditions

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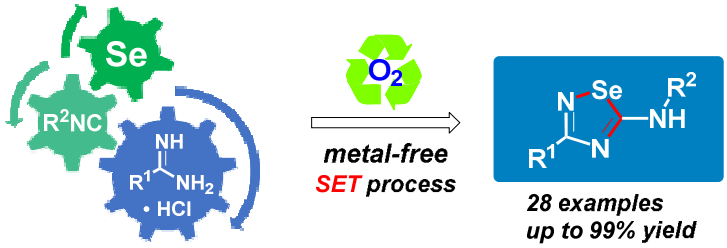

A facile and method for the synthesis of functionalized 1,2,4-selenadiazoles through aerobic radical-cascade cyclization of isocyanides, selemium and imidamides is established. The reaction proceeds smoothly under air atmosphere using O_2 as the sole oxidant. This method features good functional group compatibility, broad substrate scope, and easily available reagents. In addition, the method was successfully applied to the late-stage functionalization of biologically active molecules.