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Access to 3-alkylselenindoles by multicomponent reaction of indoles, selenium powder and unactivated alkyl halides under transition-metal-free conditions

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ABSTRACT

Herein, we reported a convenient and efficient multicomponent reaction of indoles, selenium powder and unactivated alkyl halides. This protocol provides a practical, and facile approach for the synthesis of 3-alkylselenindole derivatives. The advantages of this strategy include mild and transition-metal-free conditions, broad functional group tolerance, the use of simple and easily accessible seleniium powder and alkyl halides as coupling partners. More importantly, the reaction proceeded smoothly with a large scale (>10 g, >90% yield), which further highlighted the potential application of this selenation strategy.

Organoselenium compounds have attracted enormous attention over the past decades due to their unique biological and medicinal activities [1–5]. For example, organoselenium compound Ebselen shows excellent anti-inflammatory, anti-oxidant and cytoprotective activities [6–10], and the latest research shows that Ebselen can effectively inhibit the COVID-19 protease, which made it receive an increasing attention [11]. On the other hand, the 3-selenylindoles also exhibited unique bioactivities, such as antiproliferative activity [12], anti-inflammatory activity [13] and act as an inhibitor of tubulin polymerization [14]. Therefore, the development of a convenient and efficient method for the synthesis of 3-selenylindoles would be of important synthetic value.

In 2014, Braga and co-workers reported a microwave irradiation-assisted I_2 catalyzed selenation of indoles using diselenides as selenium source (Scheme 1a) [15]. One year later, they modified this reaction by using a catalytic amount of K_2CO_3 to give an alternative and greener protocol for the synthesis of 3-selenylindoles [16]. Unfortunately, these methods are limited to aryl diselenides, and the synthesis of 3-alkylselenindole derivatives are still challenging. Soon after, the Liu's group reported a highly efficient, visible-light-mediated aerobic selenation of indoles with diselenides (Scheme 1b) [17]. Although some dialkyl diselenides could also be successfully applied to this reaction, an expensive iridium catalyst and the pre-prepared diselenides are required for this transformation. In 2016, Wu's group reported a powerful copper-catalyzed C_3 aryl selenization of indoles using elemental selenium as the selenium source (Scheme 1c) [18]. However, a transition-metal catalyst and high temperature are required, and this method is limited to the synthesis of 3-arylselenindoles.

After that, many other protocols also provide efficient access to a wide variety of 3-selenindoles arising from different combinations of indoles and coupling partners [19–26]. However, most of the present methods are mainly focused on the synthesis of 3-arylselenindoles and the selenium source are typically limited to some pre-prepared selenating reagents. Therefore, the development of convenient and efficient approach for C_3 alkylselenization of indoles, employing easily accessible and eco-friendly selenium powder as selenium source, is highly desirable. Given our continuous interest in the divergent synthesis of biologically-relevant organoselenium compounds [27–32], herein, we reported a convenient and efficient multicomponent reaction of indoles, selenium powder and unactivated alkyl halides, which provides a practical, and facile approach for the synthesis of 3-alkylselenindole derivatives (Scheme 1d).

We initiated our studies by examining the reaction of **1a, 2** and **3a** under basic conditions. Gratifyingly, the desired product **4aa** was formed in 65% isolated yield in the presence of Cs_2CO_3. After extensive screening of a series of base and solvents (see Supporting information for details), the highest isolated yield (92%) was obtained under the optimal conditions.

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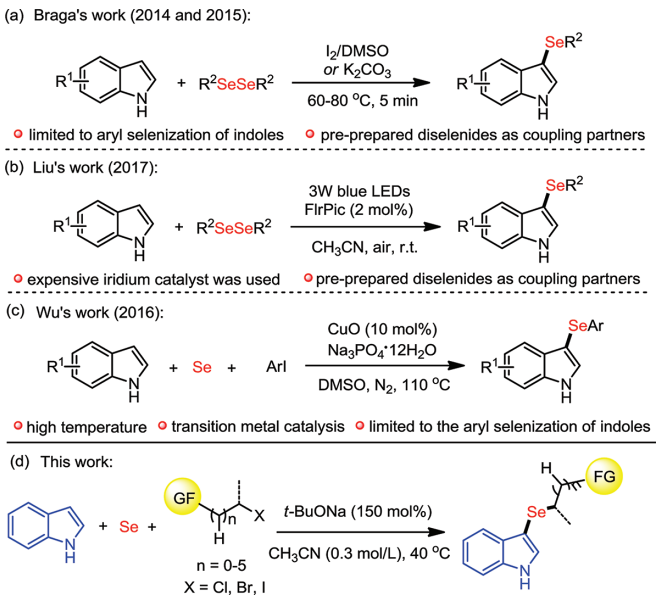
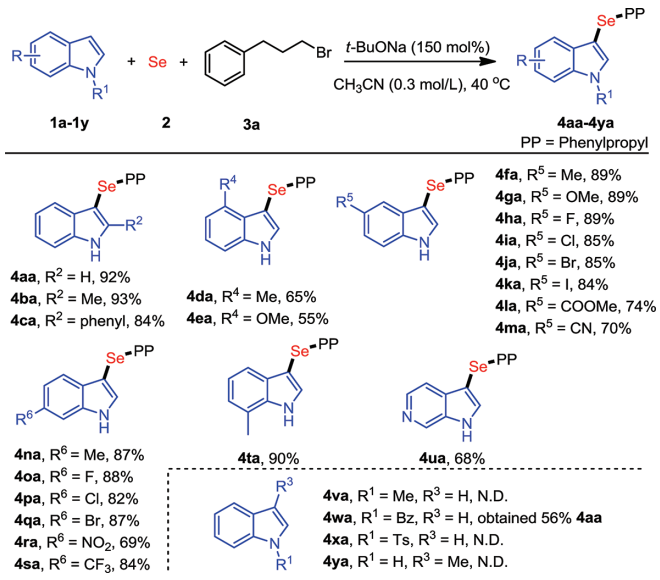
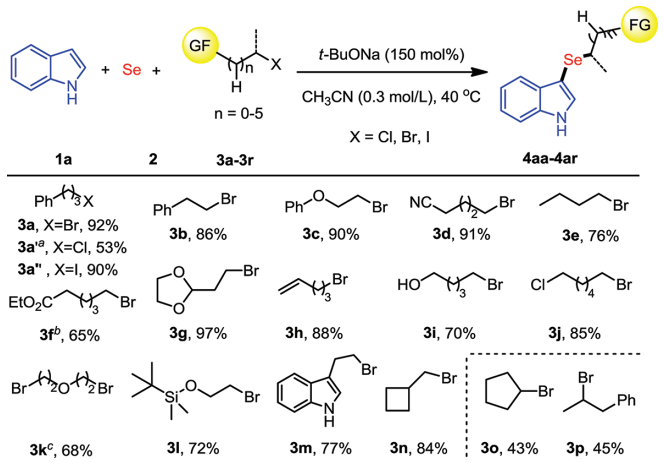


Scheme 1. Synthetic strategies for 3-selenylindoles.

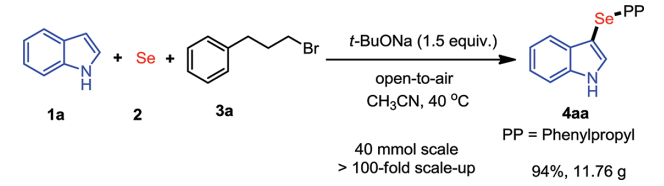


Scheme 2. Substrate scope of indoles. Reaction conditions: **1a** (0.36 mmol), **2** (0.36 mmol), **3a** (0.30 mmol), *t*-BuONa (0.45 mmol), CH_3CN (1.0 mL) at 40 °C for 6 h. Isolated yields.

With the optimized reaction conditions in hand, we firstly examined the scope and limitations of indoles **1** (Scheme 2). Satisfactorily, both substrates bearing electron-donating (**4ba–4ea, 4fa, 4na** and **4ta**) and electron-withdrawing groups (**4ha–4ma, 4oa-4sa**) could react smoothly to give the desired products in moderate to excellent yields. We investigated the reaction efficiency by changing the substituted positions of the indoles. The expected products were observed in 87%–93% yields when a methyl substituent located on the C2, C5, C6 or C7 position of indole (**4ba, 4fa, 4na** and **4ta**) were applied to the reaction. The yields were reduced slightly when 4-methylindole and 4-methoxyindole were subjected to the reaction (**4da** and **4ea**, 65% and 55%, respectively), which indicated that, compared to C2 position, C4 position had a more significant effect on C3 position from steric hindrance. Other substrates bearing electron-withdrawing groups, such as halogen (**4ha-4ka, 4oa-4qa**), ester (**4la**), cyano (**4ma**), nitro (**4ra**) and trifluoromethyl (**4sa**) moieties, were also compatible with the reaction, affording the corresponding products in 69%–89% yields. To



Scheme 3. Substrate scope of alkyl halides. Reaction conditions: **1a** (0.36 mmol), **2** (0.36 mmol), **3** (0.30 mmol), *t*-BuONa (0.45 mmol), CH_3CN (1.0 mL) at 40 °C for 6 h. Isolated yields. [a]12 h. [b]150 mol% DBU were instead of *t*-BuONa. [c]**1a** (0.72 mmol), **2** (0.72 mmol), **3k** (0.30 mmol), *t*-BuONa (0.90 mmol), CH_3CN (2.0 mL) at 40 °C for 6 h.



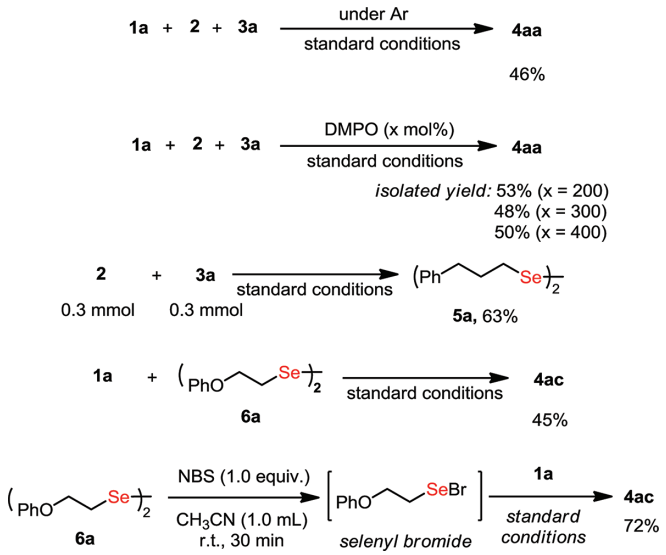
Scheme 4. Scale-up synthesis of **4aa**.

our delight, the reaction of 1*H*-pyrrolo[2,3-*c*]pyridine succeeded to furnish the desired product **4ua** in 68% yield. It is noteworthy that *N*-methyl, benzoyl, and Ts substituted indoles (**1v-1x**) failed to give the desired selenylindoles, which indicated free NH group plays a crucial role in this transformation. Among them, a deprotection product **4aa** was obtained when *N*-benzoyl indole was applied to the reaction.

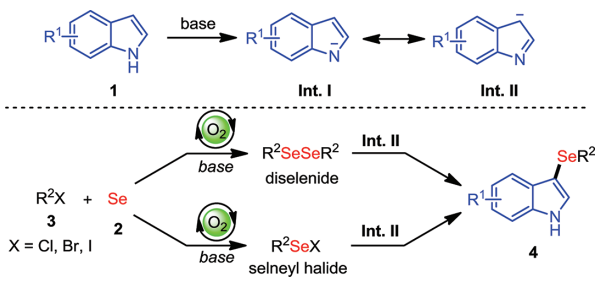
To further evaluate the generality of this strategy, we next detected the tolerance of unactivated alkyl halides (Scheme 3). In generally, a wide variety of alkyl halides bearing different functional groups worked well under standard conditions. It was found that a similar good result was obtained when alkyl iodide **3a''** was used to instead of bromide **3a**, and alkyl chloride **3a'** also performed well under standard conditions, albeit a lower yield (53%) was observed. The primary alkyl bromides containing functional groups such as ether (**3c**), cyano (**3d**), ester (**3f**), acetal (**3g**), alkene (**3h**), alcohol (**3i**), chloride (**3j**), silyl ether (**3l**) and cyclobutene (**3n**), were all well-tolerated under these mild reaction conditions. In addition, alkyl dibromide was also successfully employed to provide the diselenide product **4ak** in 68% yield. Notably, 3-(2-bromoethyl)-1*H*-indole was also tolerated under the identical reaction conditions, affording the corresponding product **4am** in 77% yield. Moreover, it was found that the secondary alkyl bromides, including cyclic and chain secondary bromides, provided the desired products **4ao** and **4ap** in lower yields (43% and 45%, respectively) alone with ~50% starting material **1a** recovered. Furthermore, tertiary alkyl bromides, such as *tert*–butyl bromide and adamantyl bromide failed to give the selenization product.

To further investigate the potential application of this multicomponent reaction, we tried to increase the reaction scale from 0.3 mmol to 40 mmol (>130-fold). To our delight, the selenization product **4aa** was still be isolated in 94% yield (11.76 g) under simple and mild conditions (Scheme 4).

To gain a deep insight into the reaction mechanism, several control experiments were carried out. Firstly, it was found that



Scheme 5. Preliminary mechanism investigation.



Scheme 6. A plausible mechanism.

the isolated yield of **4aa** was drastically reduced from 92% to 46%, when the model reaction was conducted under an argon atmosphere (Scheme 5a). This result proved that the presence of oxygen was important for this transformation. When the radical scavenger DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) was added to the system, **4aa** could still be produced smoothly. Even when DMPO was increased to 400 mol%, **4aa** could still be isolated in 50% yield (Scheme 5b). This experiment indicated that the reaction might not proceed through a radical pathway. A diselenide **5a** was obtained in 63% yield when the reaction was carried out in the absence of indole (Scheme 5c). In addition, the selenization product **4ac** was obtained in 45% yield by treating a diselenide **6a** with indole under standard conditions (Scheme 5d). Finally, it was found that the corresponding product **4ac** was obtained in 72% yield when the in-situ generated selenyl bromide species [33] was treated with indole **1a** under standard conditions (Scheme 5e). These results indicated that the diselenide or selenyl bromide specie was likely to be a key intermediate in this transformation.

On the basis of the above experimental results and previous literatures [34,35], a plausible reaction pathway is proposed to elucidate the reaction mechanism (Scheme 6). The cleavage of the acidic N-H of indole usually requires basic conditions to enable the nucleophilicity of C3 position, which generates a negative charge on the indole (**Int. II**). Probably, a diselenide intermediate or a reactive selenyl halide intermediate is generated when the alkyl halide is treated with selenium powder under basic and aerobic conditions, which would react with **Int. II** to give the corresponding 3-alkylselenindole derivatives.

In summary, we have developed an efficient selenium-transfer approach [36] for the synthesis of 3-alkylselenindole derivatives through a multi-component "one pot" reaction. Mechanistic study demonstrated that selenium powder and alkyl halides might undergo an "oxidation-addition" process to produce selenyl bromide species. This strategy efficiently synthesized various functional 3-alkylselenoindoles that have been rarely reported before under mild conditions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.01.046.

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