



Direct selenation of imidazoheterocycles and indoles with selenium powder in a copper-catalyzed three-component one-pot system



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ABSTRACT

An efficient and convenient Cu-catalyzed three-component reaction is described for the selenation of imidazoheterocycles/indoles with Se powder and aryl iodides. This procedure provides diverse 3-arylselenylimidazoheterocycles and 3-arylselenylindoles with good yields and functional group tolerance. Some of the products exhibited better or comparable antiproliferative activities compared with the positive control 5-fluorouracil against H1975, PC-9, HGC-27, EC-109, and MCF-7 cancer cell lines.

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Se-containing compounds have attracted much interest of organic and medicinal chemists over the past few years.¹ They are prevalent in diverse drug candidates and bioactive compounds with wide and interesting pharmacological properties such as anti-tumor,² antioxidant,³ anti-inflammatory,⁴ enzyme inhibitory,⁵ and antibacterial activities.⁶ In addition, organoselenium compounds are useful catalysts and crucial building blocks in organic synthesis.⁷ Furthermore, organoselenium derivatives have demonstrated great utility as fluorescent probes in materials science and optoelectronics.⁸ Therefore, it is still highly desirable to develop practical and environment-friendly synthetic methods for the introduction of stable, convenient, and economical Se reagents into organic structures (Fig. 1).

Imidazoheterocycles are widely found in medicinal agents (such as alpidem, necopidem, miroprofen, saripidem, zolpidem, and zolimidine) and considered as privileged scaffolds.⁹ Generally, the pharmacological activities of imidazoheterocycles depend on the nature of substituent at the 3-position of imidazo ring.¹⁰ Recently, much attention has been paid to incorporate Se into imidazoheterocycles to synthesize valuable 3-selenylimidazoheterocycles.¹¹ For instance, Hajra group developed a synthetic method for 3-phenylselenylimidazo[1,2-*a*]pyridines through the phenylselenylation of imidazo[1,2-*a*]pyridines using phenylselenium bromide (Scheme 1a).^{11a} Braga and co-workers reported the

synthesis of 3-selenylimidazo[1,2-*a*]pyridine derivatives by iodine-catalyzed selenation of imidazo[1,2-*a*]pyridines with diselenides.^{11b} Liu group reported a visible-light-mediated aerobic selenation of imidazo[1,2-*a*]pyridines with diselenides using FIrPic as the photocatalyst (Scheme 1b).^{11c} Recently, the use of Se powder, a stable, odorless, commercially available, and easily handled reagent, as a cross-coupling partner to construct C–Se bonds has led to the development of a more attractive and straightforward alternative Se reagent/selenation reaction.¹² The use of Se powder also allows an efficient synthesis of organoselenium compounds in terms of atom economy. To achieve a library of Se-containing compounds for drug development, our group developed a Cu-catalyzed selenation of imidazoheterocycles with Se powder and coumarinyl triflates (Scheme 1c).¹³ In continuation of our interest in the development and application of heterocycle derivatives in medicinal chemistry,¹⁴ herein, we report a Cu(OAc)₂-catalyzed selenation of imidazoheterocycles and indoles with Se powder to afford 3-selenylimidazoheterocycle and 3-selenylindole derivatives in good yields (Scheme 1d).

A model reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**), iodobenzene (**2a**), and Se powder was carried out to optimize various reaction parameters. The results are shown in Table 1. First, the reaction was carried out using CuI as the catalyst in DMSO without any additive. The desired product **3a** was obtained in 26% yield, indicating that this reaction proceeded under a neutral condition. The addition of a base and ligand helped in improving the efficiency of reaction. For example, the yield of the desired

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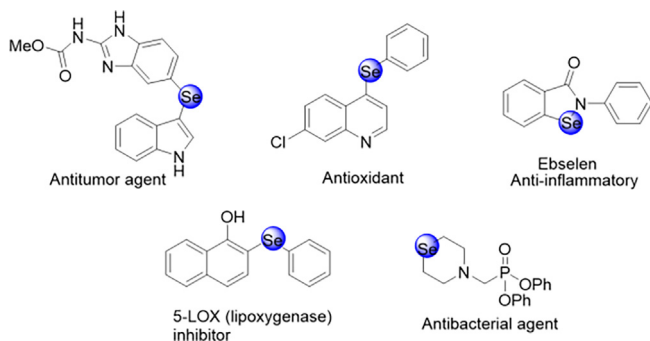


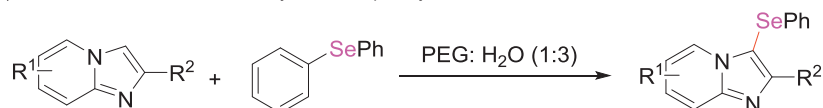
Fig. 1. Examples of biologically active organoselenides.

product **3a** increased when KOH and phen were added to **1a** (entries 2 and 3). The effect of solvents on the efficiency of reaction was investigated under similar reaction conditions. Only a trace amount of product was observed when xylenes was used as the solvent (entry 4). When NMP was used, the reaction did not proceed at all (entry 5). DMAc and 1,4-dioxane were also poor solvents for this reaction, producing product **3a** in 59% and 61% yields, respectively (entries 6 and 7). Among the solvents examined, DMF was the most effective, affording **3a** in 74% yield (entry 8). The catalyst also played a crucial role. The yields were unsatisfactory with CuSO_4 and CuO ; CuBr_2 provided **3a** in 65% yield (entries 9–11). $\text{Cu}(\text{OAc})_2$ was the most suitable catalyst, affording the desired product **3a** in 82% yield (entry 12). A screening of base was also conducted; however, when KOH was substituted with other bases such as K_3PO_4 , Na_2CO_3 , or Cs_2CO_3 , inferior results were obtained (entries 13–15). To improve the yield of reaction, the

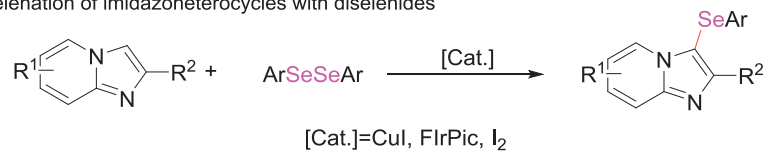
effect of ligand was evaluated. The product yield dramatically decreased when a ligand was not used (entry 16). When phen was replaced with other ligands such as bpy and 4,5-diazafluoren-9-one, lower yields were obtained (entries 17 and 18). Other factors such as reaction temperature and time were also investigated, but no improvement was achieved (entries 19 and 20). Therefore, the conditions of entry 12 were selected as the optimized reaction conditions.

With the optimized reaction conditions in hand, the substrate scope of Cu-catalyzed regioselective C-3 selenation of imidazoheterocycles **1** with Se powder and aryl iodides was investigated. The results are shown in Table 2; the reaction worked well for diverse substituted imidazoheterocycles, affording the corresponding 3-selenylimidazoheterocycle derivatives in 58–83% yields. Halogens on the benzene ring of imidazo[1,2-*a*]-pyridines were tolerated well; for example, 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine, 2-(4-chlorophenyl)imidazo[1,2-*a*]pyridine, and 2-(3-bromophenyl)imidazo[1,2-*a*]pyridine provided the desired products in 71% (**3b**), 80% (**3c**), and 65% (**3d**) yields, respectively. The presence of a strong electron-withdrawing substituent such as nitro at the phenyl ring slightly decreased the yield of **3e**. Notably, thieryl, *n*-pentyl, and cyclopropyl-substituted imidazo[1,2-*a*]pyridines were also tolerated in this catalytic system, leading to efficient synthesis of desired products **3f–3h** in 84%, 79%, and 83% yields, respectively. The yields of products **3i–3k** showed that both electron-donating and -withdrawing functionalities on the pyridine ring of imidazo[1,2-*a*]pyridine slightly affect the reaction efficiency. Moreover, this protocol could be applied to other imidazoheterocycles such as imidazo[2,1-*b*]thiazole, affording the selenation product **3l** in 67% yield. To further explore the generality of this reaction, diverse aryl iodides were examined in the reaction with 2-phenylimidazo[1,2-*a*]pyridine **1a**. Generally, under the

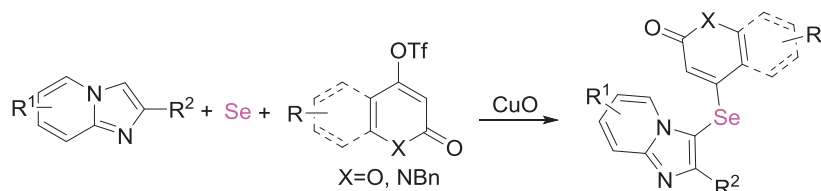
(a) Selenation of imidazoheterocycles with phenylselenium bromide



(b) Selenation of imidazoheterocycles with diselenides

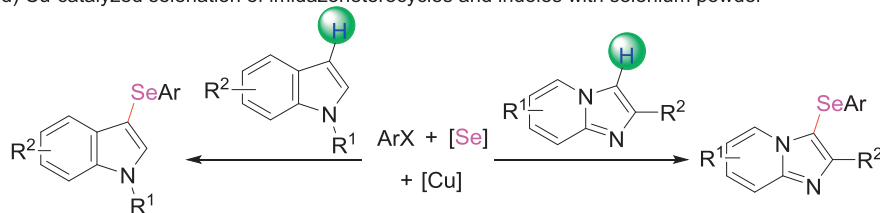


(c) Selenation of imidazoheterocycles with selenium powder and coumarinyl triflates



This work

(d) Cu-catalyzed selenation of imidazoheterocycles and indoles with selenium powder



Scheme 1. Representative methods for the selenation of imidazoheterocycles.

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