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Copper-catalyzed tandem cyclization of 2-(2-iodophenyl)imidazo[1,2-*a*]pyridine derivatives with selenium: Synthesis of benzo[*b*]selenophene-fused imidazo[1,2-*a*]pyridines

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ABSTRACT

Cu-catalyzed tandem cyclization of 2-(2-iodophenyl)imidazo[1,2-*a*]pyridines with selenium for the practical synthesis of the benzo[*b*]selenophene-fused imidazo[1,2-*a*]pyridines occurred smoothly *via* Ullmann-type *Se*-arylation and C_{sp2}–H selenation. A variety of benzo[*b*]selenophene-fused imidazo[1,2-*a*]pyridines were easily obtained in moderate-to-high yields. Single-crystal X-ray analysis of **2a** revealed that the benzo[*b*]selenophene and imidazopyridine rings are almost coplanar. The maximum absorption of tetracyclic compound **2a** was red-shifted by 45–47 nm from those of imidazo[1,2-*a*]pyridine and benzo[*b*]selenophene.

Introduction

Organoselenium compounds have attracted significant interest because of their potential as important reagents in organic synthesis and biological activities [1,2]. Transition metal-catalyzed cross-coupling reaction is one of the most popular methods to form C–Se bonds [1c,3]. Various metals including Pd, Ni, Fe, and Cu have been used to catalyze the reactions of aryl donors with a Se source. For example, Cu-catalyzed cross-coupling reactions, i.e., Ullmann-type reactions of aryl halides with selenols [4], diselenides [5], selenium powder [6], and alkyltin selenides [7] have proven to be powerful routes to C(Ar)–Se bond formation. Recently, methods for Cu-catalyzed C–Se bond formation between electron-rich heterocycles, such as imidazopyridine [8], benzothiazole [9], and indole [10] as the aryl substrate, and a Se source, such as diselenides and selenium powder, via C_{sp2}–H bond activation have been developed.

The synthesis of imidazo [1,2-*a*]pyridines and their derivatives have attracted considerable interest because of their significance in medicinal chemistry, material science, and organometallics [11]. A number of clinically used drugs and clinical candidates, such as zolpidem, alpidem, saripidem, zolimidine, necopidem, and GSK812397, contain an imidazo[1,2-*a*]pyridine scaffold [12]. The C-3 position of the imidazo[1,2-*a*]pyridine skeleton is electron-rich, which promotes attack by electrophiles. Thus, a series of Pd-, Cu-, Rh-, and Ru-catalyzed C–H functionalization reactions at the C-3 position to form a C–C bond have been achieved [13–16]. However, only a few benzoheterole-fused imidazopyridines having group 16 elements, such as benzofuro- [17] and benzothiophenoimidazo[1,2-*a*]pyridine [18], have been reported. Wang [18a] and Liu [18b] independently developed the Cu-catalyzed synthesis of benzo[*b*]thiophene-fused imidazopyridines by reacting 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine derivatives with potassium sulfide via double C–S bond formation using one-step Ullmann-type *S*-arylation and C_{sp2}–H thiolation in 2016. However, these reactions require catalyst ligands and a long reaction time (24 h) at 120–140 °C. Herein, we report efficient and simple Cu-catalyzed tandem cyclization via one-step Ullmann-type *Se*-arylation and C_{sp2}–H selenation for the synthesis of novel benzo[4′,5′]selenopheno[3′,2′:4,5]imidazo[1,2-*a*]pyridines from 2-(2-iodophenyl)imidazo[1,2-*a*]pyridine derivatives and selenium powder in the absence of additives under aerobic conditions.

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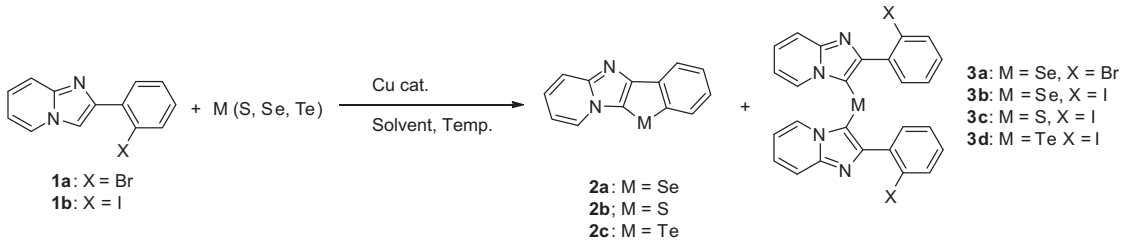
Results and discussions

We initially focused our attention on the determining the optimum conditions for the cyclization of chalcogen powders (i.e., S, Se, and Te) with 2-(2-halophenyl)imidazo[1,2-*a*]pyridines **1**. Table 1 shows the results of the screening of the substrates, catalysts, solvents, reaction temperatures, and chalcogens. We first performed cyclization reactions of Se powder with 2-(2-halophenyl)imidazopyridines **1a** and **1b** to compare the reactivity using CuI as the catalyst under aerobic conditions in DMSO at 130 °C (entries 1 and 2). The expected benzoselenophene-fused imidazopyridine **2a** was obtained in a high yield (87%) when iodide **1b** was employed as the coupling partner (entry 2). Bromide **1a** is a useful substrate as a starting material for the Cu-catalyzed synthesis of benzo[*b*]thiophene-fused imidazopyridines [18]. However, the reaction of **1a** with Se generated bis[2-(2-bromophenyl)imidazopyridin-3-yl]selenide **3a** as the main product (entry 1). Next, several available Cu(I) and (II) catalysts were screened for the reaction of **1b** with Se (entries 2–8). Among these, CuI appeared to be the best catalyst for this reaction in terms of the yield of product **2a** without by-product **3b**. Screening of solvents showed that the reaction proceeded efficiently in DMSO (87%) and NMP (64%); however, the reactions in DMF, dioxane, 1,2-DCE, CH_3CN, and toluene were inefficient (entries 2, 9–14). When the reaction was carried out at 100 °C, bis[2-(2-iodophenyl)imidazopyridin-3-yl]selenide **3b** was obtained in a 58% yield after 24 h (entry 15); this shows that it is necessary to heat the reaction mixture to 130 °C to generate benzoselenophene-fused imidazopyridine **2a**. Decreasing the loading of CuI from 10 to 5 or 1 mol% significantly reduced the yield of **2a** (entries 16 and 17). The loading of Se (2 eq) did not affect this reaction (entry 18). Thus, the best reaction condition was determined to be as follows: 2-(2-iodophenyl)imidazopyridine **1b** was treated with 1.0 eq. Se powder using 10 mol% CuI as catalyst in DMSO at 130 °C without the use of any ligand and/or inorganic reagent under aerobic conditions. We performed cyclizations using other chalcogen powders such as S and Te with 2-(2-iodophenyl)imidazopyridine **1b** under the optimized conditions (entries 19 and 20). When S powder was employed in this reaction, bis[2-(2-iodophenyl)imidazopyridin-3-yl]sulfide **3c** was generated as the major product in a 57% yield along with benzothiophene-fused imidazopyridine **2b** in a 19% yield (entry 19). The reaction of **1b** with Te powder resulted in a complex mixture (entry 20).

To demonstrate the efficiency and versatility of the determined protocol, reactions of various iodides **1** with Se powder were investigated under the optimized reaction conditions until almost the starting material was consumed. The results are summarized in Table 2. The substrates **1c-h** bearing different functional groups with electron-donating and electron-withdrawing substituents at the 6-position on the imidazopyridine ring afforded the corresponding benzoselenophene-fused imidazopyridines **4**–**7** and **9** in good-to-excellent yields except ester derivative **8**. This procedure was applicable to the synthesis of **7** with a highly reactive bromine; treatment of 6-bromo-2-(2-iodophenyl)imidazopyridine with Se gave **7** in a 78% yield with the bromine moiety remaining intact. 2-(2-Iodophenyl)imidazopyridines **1d**, **i**, **j** with methyl groups at the 6, 7, and 8-position afforded the corresponding the coupling products **5**, **10**, and **11**, respectively, in satisfactory yields.

Table 1
Cu-catalyzed cyclization of 2-(2-halogenophenyl)imidazo[1,2-*a*]pyridines **1** with chalcogen elements M.[a]



1a: X = Br
1b: X = I

2a: M = Se
2b; M = S
2c: M = Te

3a: M = Se, X = Br
3b: M = Se, X = I
3c: M = S, X = I
3d: M = Te X = I

Entry	1	M	Cu cat. (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	
							2	3
1	**1a**	Se	CuI (10)	DMSO	130	14	**2a**: 3	**3a**: 49
2	**1b**	Se	CuI (10)	DMSO	130	3	**2a**: 87	**3b**: –
3	**1b**	Se	CuBr (10)	DMSO	130	3	**2a**: 73	**3b**: –
4	**1b**	Se	CuCl (10)	DMSO	130	3	**2a**: 72	**3b**: –
5	**1b**	Se	CuOAc (10)	DMSO	130	3	**2a**: 66	**3b**: –
6	**1b**	Se	$CuBr_2$ (10)	DMSO	130	3	**2a**: 76	**3b**: –
7	**1b**	Se	$CuCl_2$ (10)	DMSO	130	3	**2a**: 74	**3b**: –
8	**1b**	Se	$Cu(OAc)_2$ (10)	DMSO	130	3	**2a**: 68	**3b**: –
9	**1b**	Se	CuI (10)	NMP	130	24	**2a**: 64	**3b**: –
10	**1b**	Se	CuI (10)	DMF	130	24	**2a**: 34	**3b**: –
11	**1b**	Se	CuI (10)	Dioxane	100	24	**2a**: 25	**3b**: –
12	**1b**	Se	CuI (10)	1,2-DCE	80	24	**2a**: 15	**3b**: –
13	**1b**	Se	CuI (10)	CH_3CN	80	24	**2a**: –	**3b**: –
14	**1b**	Se	CuI (10)	Toluene	100	24	**2a**: –	**3b**: –
15	**1b**	Se	CuI (10)	DMSO	100	24	**2a**: 7	**3b**: 58
16	**1b**	Se	CuI (5)	DMSO	130	24	**2a**: 67	**3b**: –
17	**1b**	Se	CuI (1)	DMSO	130	24	**2a**: 35	**3b**: –
18[c]	**1b**	Se	CuI (10)	DMSO	130	3	**2a**: 86	**3b**: –
19	**1b**	S	CuI (10)	DMSO	130	24	**2b**: 19	**3c**: 57
20	**1b**	Te	CuI (10)	DMSO	130	24	**2c**: –	**3d**: –

[a] Conditions: **1** (0.5 mmol), chalcogen element (0.5 mmol).
[b] Isolated yield.
[c] Se (1.0 mmol).