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FULL PAPER

Selective synthesis of 3-Selanylindoles from Indoles and Diselenides using IK/*m*CPBA system

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In the presence of a catalytic amount of KI combined with oxidant *m*CPBA, a convenient catalytic procedure is developed for the preparation of 3-selanylindoles from indoles and diselenides. In this protocol, KI is first oxidized by *m*CPBA into hypoiodous acid, which reacts with diselenide to cleave Se-Se bond. The *in situ* generated active electrophilic selenium species then reacts with indole, affording 3-selanylindole via an electrophilic substitution mechanism. This catalytic selenation of indoles has mild reaction conditions and is a simple procedure, which extends the synthetic application of KI in organic synthesis.

KEYWORDS

3-Selanylindole, catalysis, diselenide, electrophilic substitution, KI

1 | INTRODUCTION

The indole nucleus is ubiquitous in a wide range of natural products, pharmaceuticals and fine chemicals, and consequently, much attention has been paid to the synthesis of substituted indoles.[1–9] 3-Selanylindoles is a significant class of indole compounds due to they are bioactive[10–12] and potentially useful as valuable synthetic intermediates.[13–18] There are some methods for synthesis of 3-selanylindoles, besides the electrophilic cyclization of 2-alkynylanilines,[19–21] the main route for obtaining them is the use of easily available indole as starting material. Recently, using Cu-catalysts to improve the selenation of indoles has become the important methodology for the preparation of 3-selanylindoles.[22–26] Wu and co-workers reported the CuO-catalyzed three-component reaction using selenium powder as selenium source.[22] Under ultrasonic (US) irradiation, the selenation of indoles with diselenides catalyzed by CuI was also described.[23] On the other hand, using metal-like behavior of molecular iodine as catalyst, under microwave (MW) irradiation this protocol can promote the direct reaction of indoles with diselenides.[27,28] In addition, catalyst free selenation of indoles with diselenides and oxidant trichloroisocyanuric acid (TCCA) or ammonium persulfate was another method.[29,30] More recently, Braga's group demonstrated a green procedure for affording 3-selanylindoles, they fount that only adding a catalytic amount of K_2CO_3 in ethanol, the reaction of indoles with diselenides proceeded efficiently and gave the products in good yields by a radical pathway.[31] The similar protocols in ionic liquids had been also investigated before.[32,33]

These above methods, despite being versatile process, the synthesis of 3-selenylindoles and study on their potential bioactivity have not been extensively explored compared with the analogous 3-thioindoles.

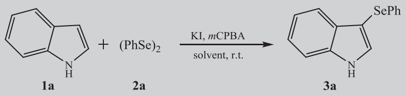
We have been interesting in oxidation and functionalization of organic compounds using hypervalent iodine reagents. In our recent research, we found that some inorganic iodides or molecular iodine can replace hypervalent iodine reagents to promote some similar reactions.[34–37] Based on this, we investigated the novel procedure for synthesis of 3-selenylindoles. Herein, we wish to report an efficient selenation of indoles with diphenyl diselenide catalyzed by KI in the presence of *m*-chloroperbenzoic acid (*m*CPBA). To the best of our knowledge, this method has not been reported before.

2 | EXPERIMENTAL

2.1 | A typical procedure for the preparation of 3-selenylindoles

Indoles **1** (0.2 mmol), diselenides **2** (0.11 mmol), KI (0.04 mmol) and *m*CPBA (0.24 mmol) were added successively to MeOH (2 ml). The suspension was vigorously stirred at r. t. for 24 h. Upon completion, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (2 mL), sat. aq. Na_2CO_3 (8 ml) and H_2O (5 ml), respectively. The mixture was extracted with CH_2Cl_2 (3 × 5 ml) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified on a silica gel plate (5:1 petroleum ether-ethyl acetate) to furnish products **3**.

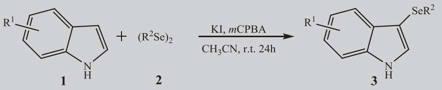
TABLE 1 Optimization of the selenation of indole (**1a**) with diselenide (**2a**) for synthesis of **3a**

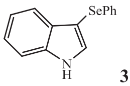
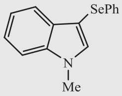
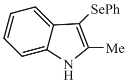
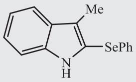
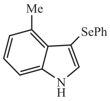
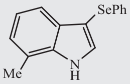
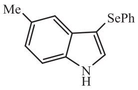
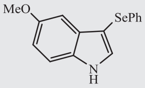
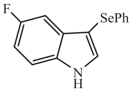
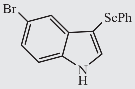
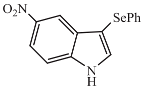
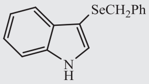
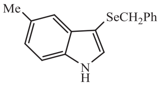
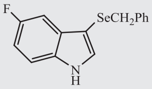


Entry	$(PhSe)_2$ (equiv)	KI (equiv)	*m*CPBA (equiv)	Solvent	Time (h)	Yield (%)[a]
1	1.1	0.2	1.2	CH_3OH	24	81
2	1.1	0.2	1.2	CH_3CN	24	94
3	1.1	0.2	1.2	CH_2Cl_2	24	72
4	1.1	0.2	1.2	CH_2ClCH_2Cl	24	66
5	1.1	0.2	1.2	EtOH	24	57
6	1.1	0.2	1.2	EtOAc	24	84
7	1.1	0.2	1.2	THF	24	88
8	1.1	0.2	1.2	DMF	24	0
9	1.0	0.2	1.2	CH_3CN	24	83
10	1.2	0.2	1.2	CH_3CN	24	92
11	2.0	0.2	1.2	CH_3CN	24	92
12	1.1	0.1	1.2	CH_3CN	24	68
13	1.1	0.5	1.2	CH_3CN	24	94
14	1.1	1.0	1.2	CH_3CN	24	92
15	1.1	NaI (0.2)	1.2	CH_3CN	24	81
16	1.1	NH_4I (0.2)	1.2	CH_3CN	24	88
17	1.1	Et_4NI (0.2)	1.2	CH_3CN	24	74
18	1.1	0.2	0.1	CH_3CN	24	24
19	1.1	0.2	0.3	CH_3CN	24	42
20	1.1	0.2	0.5	CH_3CN	24	90
21	1.1	0.2	1.0	CH_3CN	24	90
22	1.1	0.2	1.5	CH_3CN	24	90
23	1.1	0.2	TBHP (1.2)	CH_3CN	24	63
24	1.1	0.2	$KHSO_5$ (1.2)	CH_3CN	24	86
25	1.1	0.2	-	CH_3CN	24	0
26	1.1	-	1.2	CH_3CN	24	0
27	1.1	0.2	1.2	CH_3CN	6	75
28	1.1	0.2	1.2	CH_3CN	12	81
29	1.1	0.2	1.2	CH_3CN	18	84
30	1.1	0.2	1.2	CH_3CN	36	72

[a] Isolated yields.

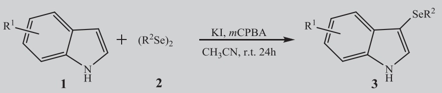
TABLE 2 Synthesis of 3-selanylindoles **3**

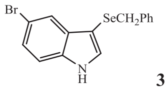


Entry	**Indoles** 1	**Diselenides** 2	**3-Selanylindoles** 3	**Yield (%)^a**
1	R^1 = H, **1a**	R^2 = Ph, **2a**	 **3a**	94
2	R^1 = 1-Me, **1b**	**2a**	 **3b**	82
3	R^1 = 2-Me, **1c**	**2a**	 **3c**	46
4	R^1 = 3-Me, **1d**	**2a**	 **3d**	25^b
5	R^1 = 4-Me, **1e**	**2a**	 **3e**	91
6	R^1 = 7-Me, **1f**	**2a**	 **3f**	82
7	R^1 = 5-Me, **1 g**	**2a**	 **3g**	87
8	R^1 = 5-MeO, **1 h**	**2a**	 **3h**	70
9	R^1 = 5-F, **1i**	**2a**	 **3i**	54
10	R^1 = 5-Br, **1j**	**2a**	 **3j**	72
11	R^1 = 5-NO$_2$, **1 k**	**2a**	 **3k**	-
12	**1a**	R^2 = PhCH$_2$, **2b**	 **3l**	85
13	**1 g**	**2b**	 **3m**	78
14	**1i**	**2b**	 **3n**	43

(*Continues*)

TABLE 2 (Continued)



Entry	Indoles 1	Diselenides 2	3-Selanylindoles 3	Yield (%)[a]
15	**1j**	**2b**	 **3o**	79

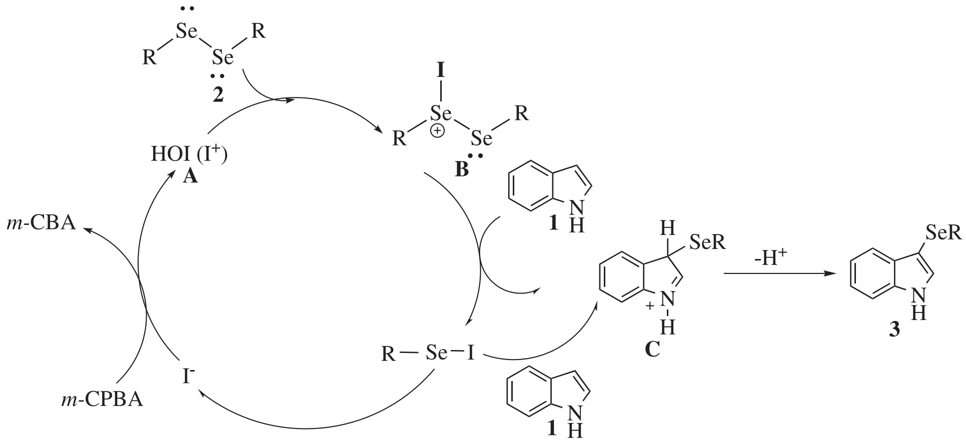
[a] Isolate yield.

[b] 2-Selanylindole **3d** was obtained.

3 | RESULTS AND DISCUSSION

Initially, we utilized indole (**1a**) and diphenyl diselenide (**2a**) as model substrates to investigate the reaction for the preparation of 3-selenylindoles in the presence of IK/*m*CPBA system at room temperature. It was found that on simple stirring of the mixture of 1.0 equiv. of **1a,** 1.1 equiv. of **2a** and 1.2 equiv. of *m*CPBA with 0.2 equiv of KI in MeOH for 24 h at room temperature in air, the expected product, 3-(phenylselanyl)-1H–indole **3a** was obtained in 81% yield (Table 1, entry 1). Then, the selenation of 1.0 equiv of **1a** with **2a** catalyzed by KI combined with *m*CPBA at room temperature was optimized. Several solvents were first evaluated, in which **3a** was obtained in the yields ranging from 57%–94% and MeCN had the best effect (entries 1–7); while using DMF as solvent, **3a** was not detected (entry 8). With MeCN as the suitable solvent, the optimized amount of **2a** was investigated, and 1.1 equiv. proved to be the best choice (entries 2, 9–11). As for catalyst KI, 0.2 equiv. of it was determined as the optimized amount (entries 2, 12–14). Similar to KI, other iodine-containing catalysts such as NaI, NH_4I and Et_4NI, all can promote the reaction and resulted in the somewhat low yields compared with KI (entries 2, 15–17). Following, the suitable amount of oxidant *m*CPBA was examined, and with 1.2 equiv. of it, the best yield of 94% was reached (entries 2, 18–22). Other oxidants, such as TBHP and $KHSO_5$ were active in the reaction in place of *m*CPBA, normally gave moderate to good yields (entries 23 and 24). As the control experiment, **3a** was not determined in the absence of *m*CPBA or KI (entries 25 and 26). Finally, the reaction time was also optimized and the results showed that in 24 hours the reaction was completed (entries 2, 27–30).

With these optimized conditions in hands, a detailed study was performed with different indoles and diselenides, showing the generality of this method (Table 2). First, the effect of methyl group on the indole nucleus was evaluated through the reaction of various methyl lindoles from **1b** to **1 g** with **2a**. It is obvious that most methyl indoles reacted with **2a** smoothly, resulting in the corresponding 3-selanylindoles **3b**, **3e**, **3f** and **3 g** in good to excellent yields (Table 2, entries 2, 5–7). 2-Methylindole **1c** also can react with **2a**; however, a low yield was obtained for **3c** due to the steric effect of neighbor methyl group (entry 3). Another methyl indole **1d** reacted with **2a** difficultly and slowly, a



SCHEME 1 Proposed mechanism for the selenation of indole catalysed by KI

much poor yield of 25% was determined for 2-selanylindole **3d**, meaning this protocol is not suitable for preparation of 2-selanylindole (entry 4). The electronic character of both electron-donating and electron–withdrawing substituents on the indole nucleus was also checked from several 5-substituented indoles, which usually had no significant influence on their reactivity (entries 7–10). However, when 5-nitroindole **1 k** was treated under the same conditions, the desired product **3 k** was not obtained (entry 11). Next, the scope of diselenide was examined. Dibenzyl diselenide **2b**, similar to **2a**, an aliphatic diselenide was also effective in the reaction, affording the corresponding products **3 l-3o** in 43–85% yields (entries 12–15). As can be seen in Table 2, except **1d** and **1 k**, all indoles provided the corresponding products were 3-selanylindoles, which indicates this catalytic selenation has a high regioselectivity.

Based on the above results and control experiments, a plausible mechanism is depicted in Scheme 1 for the catalytic selenation of indoles. KI is first oxidized by *m*CPBA into hypoiodous acid **A**, which reacts smoothly with diselenide **2** to form the active intermediate **B**, followed by a rapid of Se-Se bond cleavage.[34,38] The *in situ* generated active electrophilic selenium species then reacts with indole in an electrophilic substitution mechanism to form the unstable intermediate **C**, and after removing a proton the desired product 3-selanylindole **3** is obtained with regioselectivity. In the cycle, another active unstable intermediate ArSeI[39,40] can further transfer a second equivalent of electrophilic selenium to indole.

4 | CONCLUSIONS

In summary, we have developed a new and convenient procedure for the selective preparation of 3-selanylindoles from indoles, diselenides and *m*CPBA catalysed by KI at room temperature. This catalytic selenation of indoles has some advantages such as mild reaction conditions and simple procedure, which provides a series of 3-selanylindoles mostly in good yields. Furthermore, this reaction will extend the application scope of KI in organic synthesis.

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