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An efficient synthesis of 2-bromo(chloro)-3-selenyl(sulfenyl)indoles *via* tandem reactions of 2-(*gem*-dibromo(chloro)vinyl)anilines with diselenides(disulfides)†

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A novel and efficient synthesis of 2-bromo(chloro)-3-selenyl(sulfenyl)-indoles through tandem reactions of 2-(*gem*-dibromo(chloro)vinyl)-*N*-methylsulfonylanilines with diselenides and disulfides in the presence of *t*-BuOLi and I_2 (10 mol%) in DMSO was developed. The reactions generated the desired products in good yields with high regio-selectivity under transition-metal-free conditions in one-pot.

Organochalcogen compounds are of considerable interest in organic synthesis and the pharmaceutical industry due to their synthetic versatility and wide applications.[1] To synthesize them, dichalcogenides are often used as substrates since they are stable and easy to handle in air,[2] and the general method is based on the reaction of dichalcogenides with appropriate electrophiles, such as organic halides, acyl chlorides, *etc*.[3]

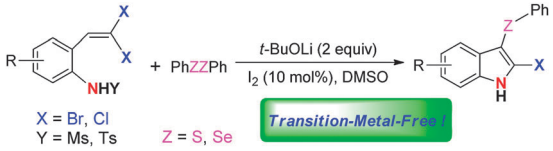
Indole derivatives are widely used as dyes, natural products, materials, and pharmaceutical ingredients, as well as starting materials for the synthesis of a large number of alkaloids.[4] Among the numerous indole nuclei, 3-selenylindoles and 3-sulfenylindoles have attracted considerable interest due to their curative effect in diseases, such as HIV, obesity, cancer, and heart disease.[5] Generally, the preparation of such compounds is achieved by the direct selenylations and sulfenylations at the 3-position of indoles. Selenylating and sulfenylating agents, such as thiols, disulfides, diselenides, selenyl and sulfenyl halides, and quinone mono-*O*,*S*-acetals, have been reported.[6] However, these methods are limited not only by the requirements of indole derivatives as starting materials, but also by the necessity of a transition-metal as catalyst.

gem-Dihaloolefins have received great attention because of their higher reactivity and ready accessibility from aldehydes.[7] Especially, the synthesis of various indole derivatives from 2-(*gem*-dibromovinyl)anilines *via* the transition-metal-catalyzed cross-coupling reactions, such as C–N/C–C,[8] C–N/C–N,[9] C–N/C–H,[10] C–N–carbonylation,[11] and C–N–carbonylation–C–C tandem reactions,[12] have been developed. Most importantly, 2-bromoindoles from 2-(*gem*-dibromovinyl)anilines for the first time *via* Pd-catalyzed intramolecular reactions by Lautens *et al*.[13]

As a part of our interest in the organic transformations of *gem*-dihaloolefins under metal-free conditions,[14] herein we wish to report a novel and efficient tandem reaction of 2-(*gem*-dibromo(chloro)vinyl)-*N*-methylsulfonylanilines with diselenides and disulfides. In the presence of *t*-BuOLi and I_2, the one-pot reactions generated the corresponding 2-bromo(chloro)-3-selenyl(sulfenyl)indoles in good yields in DMSO with high regio-selectivity under transition-metal free conditions (Scheme 1).

At the beginning of our investigation, a model reaction of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline (**1a**) with diphenyl-diselenide (**2a**) in 2 : 1 molar ratio was employed to optimize the reaction conditions and the results are summarized in Table 1. Initially, a series of bases were tested, *t*-BuOLi was found to be the best one in the presence of I_2 in DMSO (Table 1, entry 1). Na_2CO_3, K_2CO_3 and Cs_2CO_3 exhibited the comparable reactivity to *t*-BuOLi (Table 1, entries 2–4). Other bases, TBAF, Et_3N, NaOAc, K_3PO_4, *t*-BuONa, and *t*-BuOK, were less effective (Table 1, entries 5–10). Next, the effect of solvents was examined. DMSO was the best reaction media when the model reaction was carried out in the presence of *t*-BuOLi and I_2 (10 mol%). Significantly lower yields (17–41%) of **3a** were obtained when DMF, NMP, C_2H_5OH and CH_3CN were used as solvents instead of DMSO (Table 1, entries 11–14). Unfortunately, no product was detected when DCE, DME, dioxane and THF were used as solvents (Table 1, entries 15–19). When the model reaction was performed in the absence of I_2, poor yield of **3a** was obtained (Table 1, entry 20). When other 'I' sources such as HI, TBAI and ICl were used, HI gave a comparable yield of **3a** with I_2, TBAI and ICl were inferior (Table 1, entries 21–23).

Next, other *N*-substituted derivatives of 2-(*gem*-dibromovinyl)-aniline, such as *N*-benzyl, *N*-*tert*-butoxycarbonyl, *N*-acetyl, and *N*-trifluoroacetyl ones, were used instead of **1a** under *t*-BuOLi–I_2–DMSO conditions, but, no desired **3a** was detected.



Scheme 1

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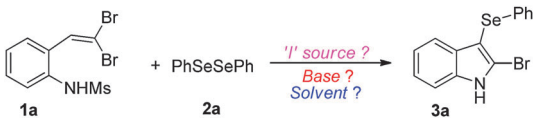
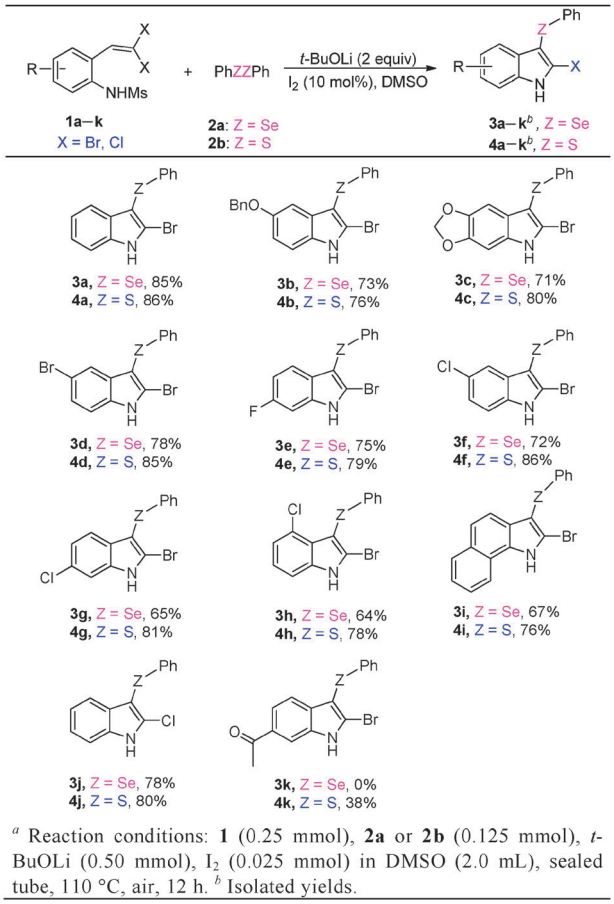
Table 1 Optimization of the reaction conditions for the model reaction of **1a** with **2a**[a]



Entry	Base	'I' source	Solvent	Yield[b] (%)
1	*t*-BuOLi	I_2	DMSO	85
2	Na_2CO_3	I_2	DMSO	75
3	K_2CO_3	I_2	DMSO	71
4	Cs_2CO_3	I_2	DMSO	69
5	TBAF	I_2	DMSO	34
6	Et_3N	I_2	DMSO	27
7	NaOAc	I_2	DMSO	25
8	K_3PO_4	I_2	DMSO	21
9	*t*-BuONa	I_2	DMSO	15
10	*t*-BuOK	I_2	DMSO	12
11	*t*-BuOLi	I_2	DMF	41
12	*t*-BuOLi	I_2	NMP	34
13	*t*-BuOLi	I_2	C_2H_5OH	28
14	*t*-BuOLi	I_2	CH_3CN	17
15	*t*-BuOLi	I_2	Toluene	0
16	*t*-BuOLi	I_2	DCE	0
17	*t*-BuOLi	I_2	DME	0
18	*t*-BuOLi	I_2	Dioxane	0
19	*t*-BuOLi	I_2	THF	0
20	*t*-BuOLi	—	DMSO	23
21	*t*-BuOLi	HI	DMSO	79
22	*t*-BuOLi	TBAI	DMSO	38
23	*t*-BuOLi	ICl	DMSO	26

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), base (1.0 mmol), 'I' source (0.050 mmol), solvent (2.0 mL), sealed tube, 110 °C, air, 12 h. [b] Isolated yields.



[a] Reaction conditions: **1** (0.25 mmol), **2a** or **2b** (0.125 mmol), *t*-BuOLi (0.50 mmol), I_2 (0.025 mmol) in DMSO (2.0 mL), sealed tube, 110 °C, air, 12 h. [b] Isolated yields.

Scheme 2 The reactions of 2-(*gem*-dibromo(chloro)vinyl)-*N*-methylsulfonylanilines with diphenyldiselenide(disulfide)[a].

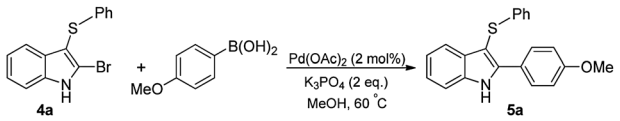
2-(*gem*-Dibromovinyl)-*N*-(*p*-tolylsulfonyl)aniline was inferior to **1a**, and generated **3a** in 72% yield. When 2-(*gem*-dibromovinyl)-aniline was used instead of **1a**, the reaction did not occur. The results indicated that this tandem reaction depends on the nitrogen substituents of substrates. When the amine is activated by a strong electron-withdrawing group such as sulfonyl, the tandem reaction can occur efficiently in one-pot. Here, the sulfonyl linker serves as a dual-activating group to undergo indole cyclization.

Under the optimized conditions, the reaction scope of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines (**1**) with 1,2-diphenyldiselenide (**2a**) was examined. Substrates **1** with the electron-donating groups on the benzene rings reacted with **2a** smoothly and generated the corresponding products in good yields (Scheme 2, **3b, 3c, 3i**). Halogen substituents on the aromatic rings of **1d**–**h** were also tolerated, affording good yields of polyhalogenated indole derivatives **3d**–**h**, which provides an attractive route for their further transformation into natural and unnatural product skeletons *via* transition-metal-catalyzed reactions. It is obvious that there is no *ortho*-position effect of **1** in the tandem reactions (**3h** and **3i**). Notably, 2-(*gem*-dichlorovinyl)-*N*-methylsulfonylaniline (**1j**) could also proceed with the tandem reaction to generate the corresponding product **3j** in good yield under the present reaction conditions. However, 2-(*gem*-dibromovinyl)-*N*-methylsulfonylaniline **1k** with an electron-withdrawing substitution on the aromatic ring did not proceed the reaction with **2a** (Scheme 2, **3k**).

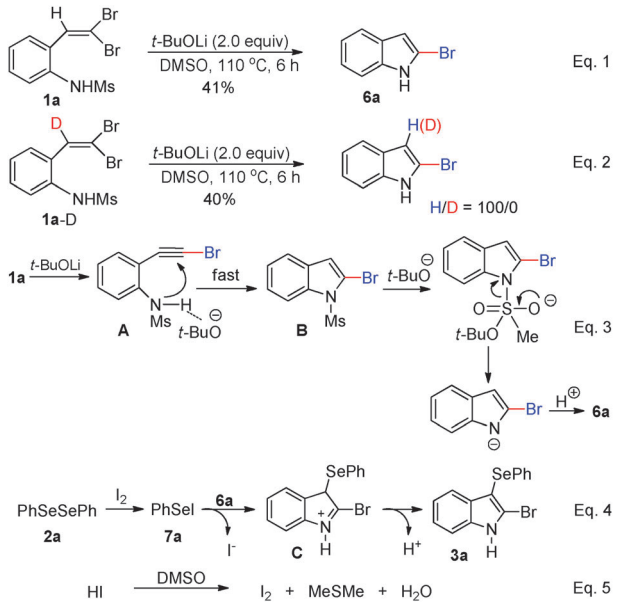
On the other hand, the tandem reaction of **1** with diphenyldisulfide (**2b**) was also examined. The results indicated that substrates **1**, without a substituted group or bearing the electron-donating groups on the aromatic rings, also conducted the reactions smoothly and afforded the corresponding products in good yields (Scheme 2, **4a**–**j**). 2-(*gem*-Dichlorovinyl)-*N*-methylsulfonylaniline (**1j**) also reacted with **2b** to generate **4j** in 80% yield. It is worth mentioning that *gem*-dibromoolefins with the electron-withdrawing substitution on the aromatic ring could react with **2b**, but, the product yield was low (Scheme 2, **4k**). However, the present method was not suitable for alkyl disulfides.

To further investigate the application of the obtained products through transition-metal-catalyzed organic transformation, **4a** reacted with 4-methoxyphenylboronic acid under the classic Suzuki reaction conditions, and the cross-coupling product **5a** was obtained in 92% yield (Scheme 3). This transformation is an introduction of an aryl group to the 2-position of **4a** *via* carbon–carbon formation to afford a complicated indole scaffold.

When the reaction of **1a** in the absence of **2a** or **2b** was performed under *t*-BuOLi–DMSO conditions without I_2, an intermediate 2-bromoindole (**6a**) was isolated in 41% yield (Scheme 4, eqn (1)). To further investigate the reaction mechanism, the isotope experiments were conducted. When the reaction of deuterium-labeled **1a-D** was performed in DMSO–*t*-BuOLi, **6a** was obtained in 40% yield and 100% D-enriched element was lost in the product (Scheme 4, eqn (2)). These results suggested that the intramolecular tandem cyclization of **1a** was through a key intermediate phenylethynyl bromide,[15]



Scheme 3 Suzuki reaction of **4a** with 4-$MeOC_6H_4B(OH)_2$.



Scheme 4 Proposed reaction mechanism and related experiments.

which could not be isolated owing to the fast reaction of **A** to **B**. The reaction process for the generation of **6a** was through an elimination of HBr from **1a** to intermediate **A** in the presence of *t*-BuOLi, followed by an intramolecular nucleophilic addition of nitrogen to the carbon–carbon triple bond of **A** to give intermediate **B**, which underwent a cleavage of the sulfonamide linkage with the assistance of *t*-BuO^- to generate **6a** (Scheme 4, eqn (3)). For the sequential 3-selenylation of **6a**, the reaction of PhSeSePh (**2a**) with I_2 afforded an electrophilic species PhSeI (**7a**), which was followed by an electrophilic addition to the indole moiety, providing intermediate **C**. After deprotonation of **C**, the final product **3a** was generated, along with the release of HI, which was oxidized by DMSO to generate H_2O, dimethylsulfide and regenerated I_2 for the next run (Scheme 4, eqn (4) and (5)).[16] For further verification, the obtained **6a** was reacted with **2a** under the present reaction conditions, giving **3a** in 92% yield.

In conclusion, a novel, efficient and facile route for the synthesis of 2-bromo-3-selenylindoles and 2-bromo-3-sulfenylindoles *via* a tandem one-pot reaction of 2-(*gem*-dibromovinyl)-*N*-methylsulfonylanilines with diphenyldiselenide and diphenyldisulfide was developed. The reactions were carried out in the presence of *t*-BuOLi in DMSO, combined with a catalytic amount of I_2 under transition-metal-free conditions, and generated the desired products in good yields with high regio-selectivity. The reaction was also extended to the preparation of 2-chloro-3-selenylindoles and 2-chloro-3-sulfenylindoles from the corresponding 2-(*gem*-dichlorovinyl)-*N*-methylsulfonylanilines. Further investigation on the application of this strategy and a detailed reaction mechanism is currently underway.

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