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PIFA-mediated selenylative spirocyclization of indolyl ynones: facile access to selenated spiro[cyclopentenone-1,3′-indoles]†

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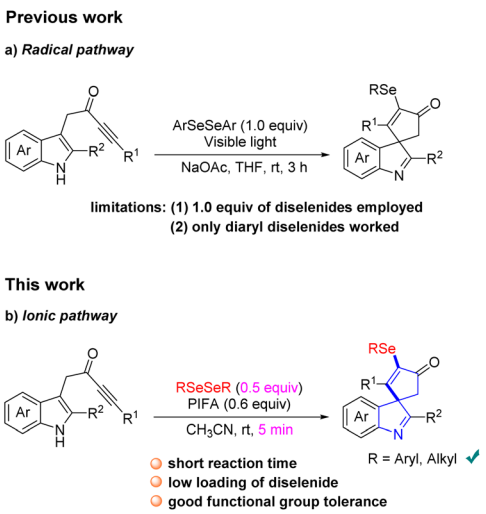
A fast selenylative spirocyclization of indolyl ynones mediated by PIFA has been developed. This transformation was enabled by the reactive $RSeOCOCF_3$ species generated *in situ* from diselenides with PIFA, involving an electrophilic dearomative cascade cyclization. This protocol provides a facile and efficient method for the synthesis of selenated spiro[cyclopentenone-1,3′-indoles] and tolerates broad functional groups.

Introduction

Spirocycles are ubiquitous in numerous pharmaceuticals, natural products, and valuable materials.[1] Among the spirocycles, spiroindolenines have aroused great interest from organic chemists lately because of their diverse biological activities.[2] Hence, development of efficient protocols for the direct construction of spiroindolenines is highly valuable in modern organic synthesis.[3] In recent years, dearomative cascade cyclization with indolyl ynones has emerged as a powerful tool for the synthesis of sophisticated spiroindolines.[4] For example, Unsworth[4a–c] and Van der Eycken[4d] described an efficient transition metal-catalyzed or trifluoroacetic acid (TFA)-promoted monofunctionalization of indolyl ynones to access spiroindolines, respectively. Subsequently, some elegant bifunctionalizations of indolyl ynones for the construction of functionalized spiroindolenines have been disclosed by organic chemists.[4e–j] Although several methods for the synthesis of the spiroindolenine scaffold have been well established, the facile and efficient construction of diverse functionalized spiroindolines is still in high demand.

On the other hand, organoselenides are an important class of bioactive molecules extensively found in pharmaceuticals and biologically active compounds.[5] So far, a great deal of effort has been devoted to investigating the preparation of organoselenides.[6] Among which, the diselenides are the most commonly used selenization reagents for these transformations.[7] Considering the importance of spiroindoline and selenium in medicinal chemistry, efficient strategies for the synthesis of selenated spiroindolenines with potential biological interest are valuable. Recently, Xu's group realized an elegant visible light-promoted selenylative spirocyclization of indolyl ynones toward the formation of seleno-spiroindolenines *via* an arylselenyl radical process (Scheme 1a).[8] Despite simple and mild reaction conditions, this method suffers from several limitations: (1) low atom economy of the reaction since only half equivalent of diselenide was utilized and the other half equivalent was wasted. (2) the diselenide bearing an alkane moiety was incompatible in the current transformation. Therefore, developing a new synthetic methodology with low loading of diselenide and high functional group tolerability to access seleno-spiroindolenines was necessary. Very recently, Zhao and Du disclosed that the reactive $RSeOCOCF_3$ species generated *in situ* from diselenides with PIFA, which could participates in an



Scheme 1 Synthesis of selenated spiroindolenines *via* radical or ionic process.

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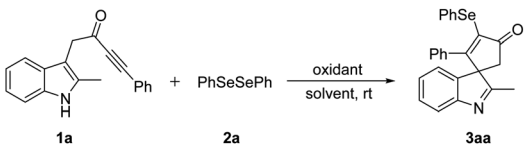
electrophilic cyclization as an electrophile.[9] Inspired by above results and our continuing interest in the construction of spirocycles and nitrogen-containing heterocyclics,[10] herein, we report a fast PIFA-mediated selenylative spirocyclization of indolyl ynones for the construction of selenated spiroindolenines under mild conditions, involving an ionic pathway with a electrophilic cyclization (Scheme 1b). This reaction was enabled by $RSeOCOCF_3$ generated *in situ* from diselenides with PIFA, followed by an electrophilic dearomative cascade cyclization of indolyl ynones.

We commenced our investigation with the reaction of indole ynone **1a** (0.2 mmol), diphenyl diselenide **2a** (0.5 equiv.), and PIFA (0.6 equiv.) at room temperature under air atmosphere in DCM. To our delight, the desired product **3aa** was afforded in 71% yield (Table 1, entry 1). First, various solvents were tested (entries 2–7), and acetonitrile (CH_3CN) was found to be optimal (entry 4). Other hypervalent iodine oxidants including PIDA, $PICl_2$ gave inferior yields of **3aa** (entries 8–9). In addition, tuning the loading of PIFA did not further improve the reaction (entries 10 and 11). Control experiment indicated that no reaction occurred in the absence of PIFA (entry 12).

After identifying the optimal reaction conditions, the substrate scope in this PIFA-mediated selenylative spirocyclization was investigated. The scope of diselenides **2** was first surveyed to react with indole ynone **1a** (Table 2). Diselenides **2** bearing electron-donating groups, such as me, et, meo, and *t*-Bu at the *para* position of the phenyl ring, leading to the corresponding products in 87–89% yield (**3ab–3ae**). The reaction could also be scaled up to 4 mmol to give 1.42 g (83%) of product **3aa**. *para*-Halogen-substituted substrates, such as F, Cl, and Br, afforded the desired products in 84–91% yield (**3af–3ah**). *meta*-Substituted diselenides with either electron-donating group (MeO) or electron-withdrawing group (CF_3) were also worked well, giving spiroindolenines **3ai** and **3aj** in 80 and 85% yields, respectively. Furthermore, substituent at the *ortho*-position also proved to be tolerated and the corresponding product **3ak** was generated in 74% yield. Diselenide bearing a thiophene moiety was also tolerated, giving **3al** in 77% yield. The naphthyl-substituted selenated spiroindolenine **3am** was afforded in 73% yield. In addition, dialkyl diselenides also served as suitable reaction partners with indole ynone **1a**, giving the desired products **3an** and **3ao** in excellent yields.

Next, various indolyl ynones **1** were tested with diphenyl diselenide **2a** (Table 3). The effect of the substituents on the phenyl ynones was first explored. In general, this procedure was

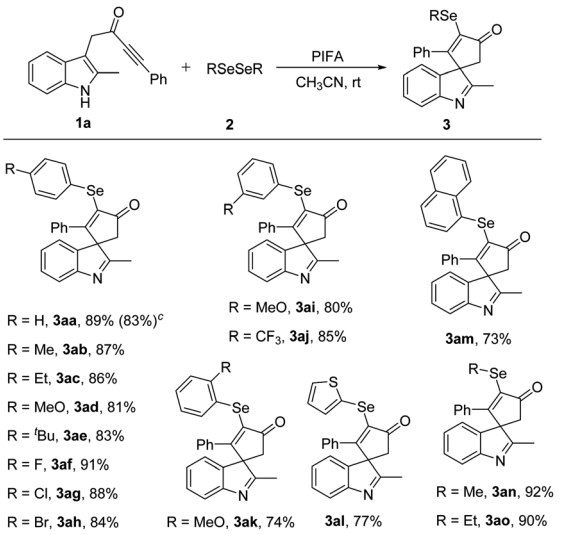
Table 1 Optimization of the reaction conditions[a,b]



Entry	Oxidant	Solvent	Yield(%)[b]
1	PIFA	DCM	71
2	PIFA	DCE	74
3	PIFA	THF	56
4	PIFA	CH_3CN	89
5	PIFA	DMSO	33
6	PIFA	MeOH	Trace
7	PIFA	Toluene	65
8	PIDA	CH_3CN	NR
9	$PhICl_2$	CH_3CN	75
10[c]	PIFA	CH_3CN	66
11[d]	PIFA	CH_3CN	86
12	—	CH_3CN	NR

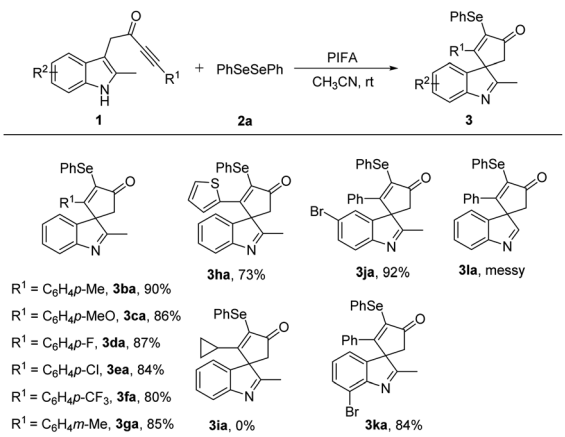
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), and oxidant (0.12 mmol) in solvent (2 mL) at rt for 5 min. [b] Isolated yield. [c] PIFA (0.1 mmol) was used. [d] PIFA (0.16 mmol) was used.

Table 2 Scope of diselenides[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), 2 (0.1 mmol), and PIFA (0.12 mmol) in CH_3CN (2 mL) at rt for 5 min. [b] Isolated yield. [c] 4 mmol scale.

Table 3 Scope of indolyl ynones[a,b]

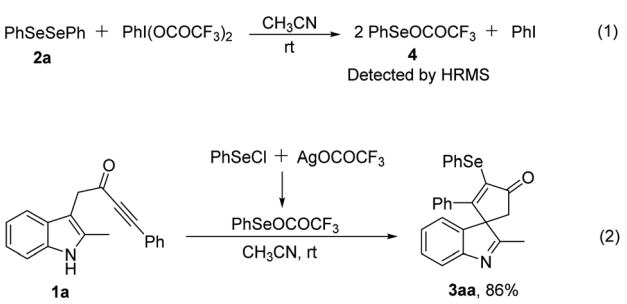


[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.1 mmol), and PIFA (0.12 mmol) in CH_3CN (2 mL) at rt for 5 min. [b] Isolated yield.

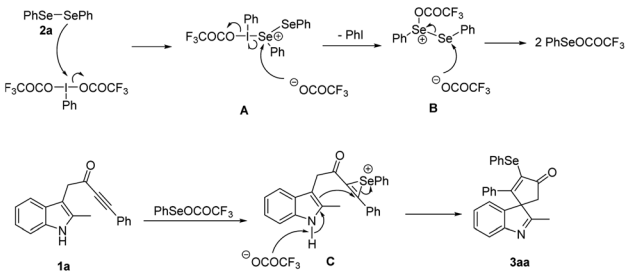
compatible with methyl, methoxy, halide, and trifluoromethyl groups, which gave the desired products **3ba–3ga** in 80–90% yield. However, *ortho*-substituted aryl alkynes as substrates, such as *ortho*-bromo-substituted aryl alkyne, there was no reaction occurred and no desired product was obtained. Additionally, 2-thienyl in the alkyne reacted smoothly to provide **3ha** in satisfactory yield. When the aryl group of ynones was replaced by an alkyl group, such as cyclopropyl, no desired product **3ia** was detected. Then, the effect of the substituents on the indole ring (R^2) was studied, the substrates with a group at the C5 or C7 position of the indole ring were all tolerated (**3ja–3ka**). The substrate with a methoxy group at the C4 position of the indole ring treated with **2a** affording a trace amount of desired product, perhaps due to the steric hindrance at the C4-position was unfavorable for the dearomatizing spirocyclization. Meanwhile, when the methyl group on the indole skeleton rings replaced with a phenyl group, the substrate 1 failed to transform into desired product, perhaps aslo due to the steric hindrance at the C2-position was unfavorable for the transformation. Unfortunately, when non-two-substituted indole in the substrate **1** was used, the reaction failed to give the desired product **3la**.

To understand the reaction mechanism, we carried out several control experiments. First, when PIFA and diphenyl diselenide reacted at rt in the absence of substrate **1a**, leading to compound **4**, which was detected by HRMS (see the ESI†) (Scheme 2, eqn 1). Moreover, when substrate **1a** was treated with PhSeCl and silver trifluoroacetate in acetonitrile at room temperature,[11] the desired product **3aa** was obtained in 86% yield (Scheme 2, eqn 2). Both control experiments indicated that this transformation was enabled by the reactive $RSeOCOCF_3$ species generated *in situ* from diselenides with PIFA.

Base on the above results and previous reports,[9,12] a plausible reaction pathway is shown in Scheme 3. First, the oxidation of diselenide **2a** by PIFA promotes the generation of reactive $PhSeOCOCF_3$ through the attack of selenium of diselenide on the iodine center of PIFA to form intermediate **A**, which was converted to selenium salt **B** after the elimination of PhI. Then trifluoroacetic acid anion attacked the selenium atom of salt B to produce two molecules of $PhSeOCOCF_3$. Next, $PhSeOCOCF_3$ reacted with the alkyne group of indolyl ynone **1a** leaded the formation of selenium ion **C**. Finally, the electrophilic dearomative cyclization of C at 3-position of indole to give the desired product **3aa**.



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.

Conclusions

In summary, a selenylative spirocyclization of indolyl ynones mediated by PIFA has been developed. This protocol provides a simple, high-yielding approach for the quick formation of selenated spiroindolenines. The reaction requires mild conditions and shows broad reactivity. Exploration of the reaction mechanism suggests that an electrophilic $RSeOCOCF_3$ -induced dearomative cascade cyclization is the operative reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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