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A formal intermolecular [4 + 1] cycloaddition reaction of 3-chlorooxindole and *o*-quinone methides: a facile synthesis of spirocyclic oxindole scaffolds†

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Herein, we developed an efficient and straightforward method for the rapid synthesis of spirocyclic oxindole scaffolds *via* the [4 + 1] cyclization reaction of 3-chlorooxindole with *o*-quinone methides (*o*-QMs), which were generated under mild conditions. The products could be obtained in excellent yields with numerous types of 3-chlorooxindole. This methodology features mild reaction conditions, high atom-economy and broad substrate scope.

The structural diversity of spirocyclic oxindole scaffolds is a reason for their frequent occurrence in many relevant natural products and medicinal agents (Fig. 1).[1] In particular, natural spirocyclic-2-oxindole scaffolds have been proven to exhibit a broad range of biological activities and have attracted increasing attention in the synthetic field. For instance, XEN 907 is a novel pentacyclic spirooxindole with excellent activities as sodium channel blockers.[2] Due to their unique structure and intriguing biological activity, numerous methodologies have been developed for the construction of these privileged frameworks.[3] For example, in the past few years, transition-metal catalyzed or organocatalytic [3 + 2] cycloaddition reactions have been developed for the synthesis of spirocyclic oxindole scaffolds.[4] Despite the emergence of these elegant approaches, exploiting new strategies for the construction of spirocyclic oxindole derivatives is still highly desirable.

Ortho-quinone methides (*o*-QMs) as highly reactive versatile intermediates have been of great interest to the chemical and biological community.[5] *o*-QMs react with various classes of reagents by three typical reaction pathways: 1,4-addition of nucleophiles, [4 + 2] cycloaddition with dienophiles and oxa-6π-electrocyclization.[6] Because most *o*-QMs are unstable, these reactions generally depend on the reaction conditions used for the generation of *o*-QMs *in situ*. Rokita *et al.* reported that *o*-silylated phenols when exposed to fluoride could also produce *o*-QMs under mild reaction conditions.[7]

Because of the dual nature (nucleophilic/electrophilic) of the C-3 position, 3-chlorooxindole serves as a highly reactive starting material in the synthesis of spirocyclic oxindole scaffolds. The introduction of a chloro group at the C-3 position of indoles serves as an excellent leaving group in favour of the subsequent cyclization. In addition, this also increases the acidity of the C–H bond for directly entering the C-3 quaternary centers.[8] Inspired by this reactivity profile, 3-chlorooxindoles have been successfully utilized for [2 + 1][9] and [4 + 1][10] cyclization to synthesize spirocyclic oxindole scaffolds (Fig. 2).

We designed an efficient and straightforward method for the rapid synthesis of spirocyclic oxindoles *via* the [4 + 1] cyclization reaction of 3-chlorooxindole with *o*-QMs, which were generated under mild conditions. In this study, using TBAF as the fluoride source and base ensures that the one-pot domino reaction will occur in mild reaction conditions, with high atom-economy and broad substrate scope.

Initially, we carried out optimization studies by examining the reaction between O-silylated phenol **2a** and 3-chlorooxindole **1a**. Indeed, when TBAF was employed as the fluoride source, a smooth [4 + 1] cyclization reaction occurred, affording the spirocyclic oxindole product **3a** with 75% yield (entry 1,

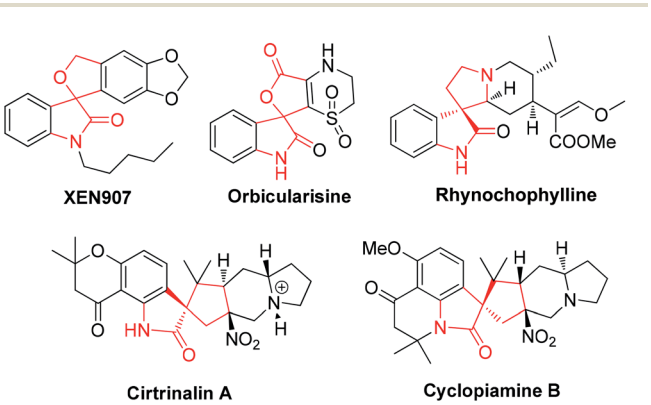

Fig. 1 Examples of biologically active spirocyclic oxindole scaffolds.

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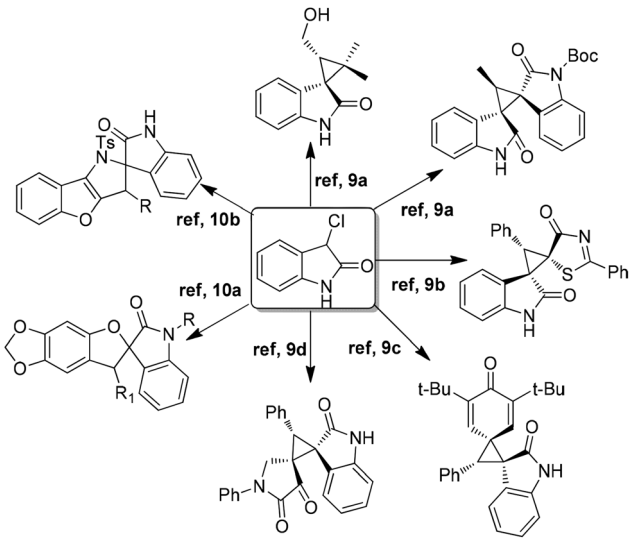
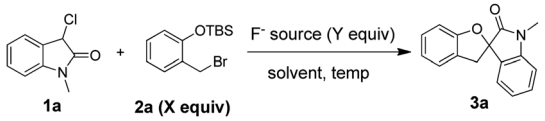


Fig. 2 Representation of the synthesis and applications of 3-chlorooxindoles.

Table 1). This indicated that our design for the [4 + 1] cyclization reaction required is feasible. When the molar concentration of substrate **2a** was raised to 1.5 equiv., the product yield increased to 87% (entry 2, Table 1). Other fluoride sources were then evaluated and TBAF was found to be the optimal one; however, when CsF was employed in this reaction, the product yield decreased to 11% (entry 4, Table 1). When the loading quantity of TBAF was decreased to 3.0 equiv., the desired product **3a** yield decreased to 80% (entry 5, Table 1). Finally, numerous solvents including $CHCl_3$, THF, toluene, DMF, MeCN, and MeOH were tested at room temperature, revealing THF as the optimal solvent for this reaction, affording the spirocyclic oxindole product **3a** with 94% yield (entries 6–11, Table 1).

With the optimal conditions known, we next investigated the substrate scope of substituted 3-chlorooxindole **1** using O-silylated phenol **2a** as a representative (Table 2). First, we

Table 1 Optimization of the reaction conditions[a]



Entry	F^- source	*X*	*Y*	Solvent	Temp (°C)	Yield[b]
1	TBAF[c]	1.2	4.0	DCM	rt	75%
2	TBAF	1.5	4.0	DCM	rt	87%
3	TBAF	2.0	4.0	DCM	rt	85%
4	CsF	1.5	4.0	DCM	rt	11%
5	TBAF	1.5	3.0	DCM	rt	80%
6	TBAF	1.5	4.0	$CHCl_3$	rt	83%
7	TBAF	1.5	4.0	THF	rt	94%
8	TBAF	1.5	4.0	Toluene	rt	90%
9	TBAF	1.5	4.0	DMF	rt	72%
10	TBAF	1.5	4.0	MeCN	rt	84%
11	TBAF	1.5	4.0	MeOH	rt	ND

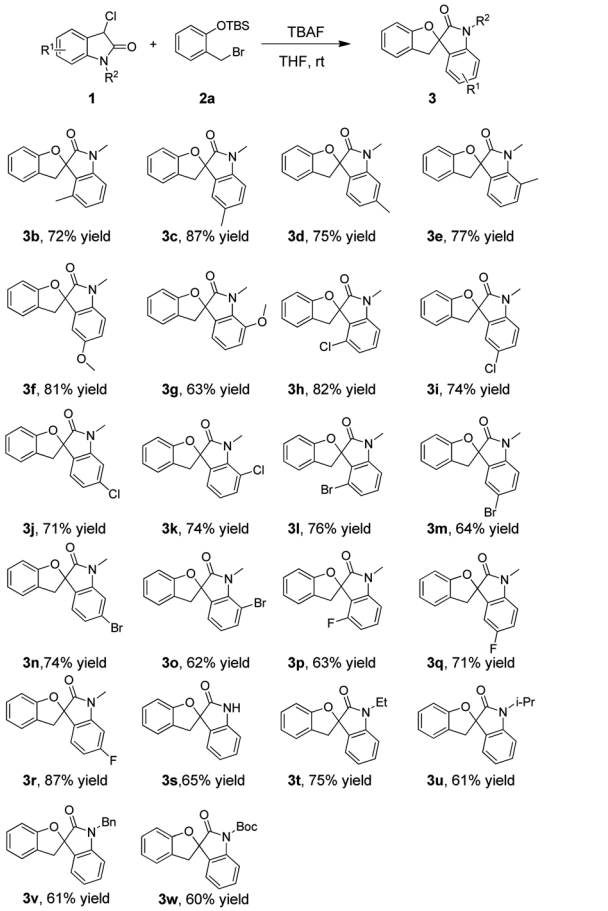
[a] Reaction conditions: **1a** (0.3 mmol), solvent (3.0 mL), 6 h. [b] Isolated yield. [c] TBAF (1 M in THF solution).

examined the substituents on the benzene ring of the indole core regardless of the electronic properties, such as 4-Me, 5-Me, 6-Me, 7-Me, 5-OMe, 7-OMe, 4-Cl, 5-Cl, 6-Cl, 7-Cl, 4-Br, 5-Br, 6-Br, 7-Br, 4-F, 5-F and 6-F. We found that all the reactions could proceed smoothly, affording the corresponding products generally with good yields (62–87%). Second, the substrates **1s** with hydrogen atoms linked to the nitrogen were all tolerated to furnish the corresponding products in moderate yields (65%). Finally, different alkyl substituents at the nitrogen position of 3-chlorooxindole **1** did not affect the outcome significantly and gave the products **3t**–**3v** in well-tolerated yields. For example, the reaction of the ethyl-substituted derivative **1t** with **2a** afforded the desired product **3t** in 75% yield.

Next, we also explored the substrate scope of substituted 3-chlorooxindole **1** using O-silylated phenols **2a′** (Table 3). When the substrate **2a′** was substituted with a chlorine atom, the yield of the desired product **3** yield decreased to 50–62%. For all the obtained products, the substrates **2a** had an influence on reaction yield.

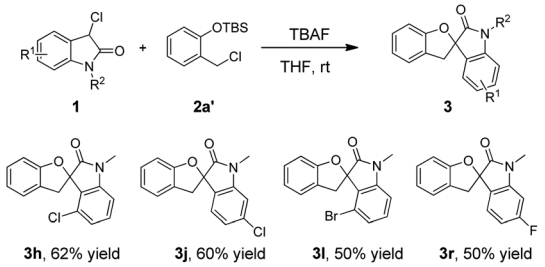
On the basis of above-mentioned results, a plausible mechanism for this formal [4 + 1] cycloaddition reaction is depicted in Scheme 1. Initially, the highly reactive *o*-QMs are generated

Table 2 Substrate scope[a,b]

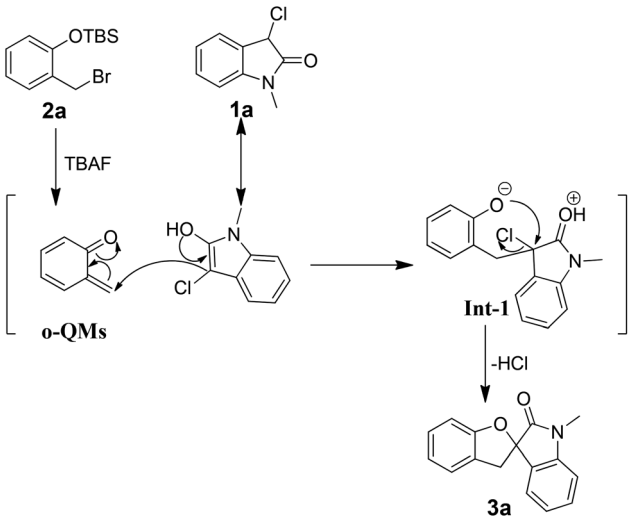


[a] Reaction conditions: **1** (0.3 mmol), **2a** (1.5 eq.), TBAF (4.0 eq.), THF (3.0 mL), 6 h. [b] Isolated yields.

Table 3 Substrate scope[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2a′** (1.5 eq.), TBAF (4.0 eq.), THF (3.0 mL), 6 h. [b] Isolated yields.



Scheme 1 Possible mechanism.

via the desilylation/elimination reaction. Then, 3-chlorooxindole **1a** as a nucleophile attacks the external carbon of *o*-QMs, affording zwitterion Int-1. Finally, the zwitterion Int-1 loses one molecular HCl through a nucleophilic attack, yielding the spirocyclic oxindole product **3a**.

Conclusions

In summary, we have established a formal [4 + 1] cycloaddition reaction of 3-chlorooxindole with O-silylated phenols. This transformation provides an efficient method for the synthesis of the spirocyclic oxindoles in good yields (up to 94%). This methodology features mild reaction conditions and a broad substrate scope.

Conflicts of interest

There are no conflicts to declare.

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