


 Cite this: *RSC Adv.*, 2021, 11, 18576

 Received 9th February 2021  
Accepted 8th May 2021

DOI: 10.1039/d1ra01086g

[rsc.li/rsc-advances](https://rsc.li/rsc-advances)

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

 Chao Lin, \* Qi Xing and Honglei Xie\*

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).<sup>1</sup> 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.<sup>2</sup> Due to their unique structure and intriguing biological activity, numerous methodologies have been developed for the construction of these privileged frameworks.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> *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-6 $\pi$ -electrocyclization.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8</sup> Inspired by this reactivity profile, 3-chlorooxindoles have been successfully utilized for [2 + 1]<sup>9</sup> and [4 + 1]<sup>10</sup> 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,

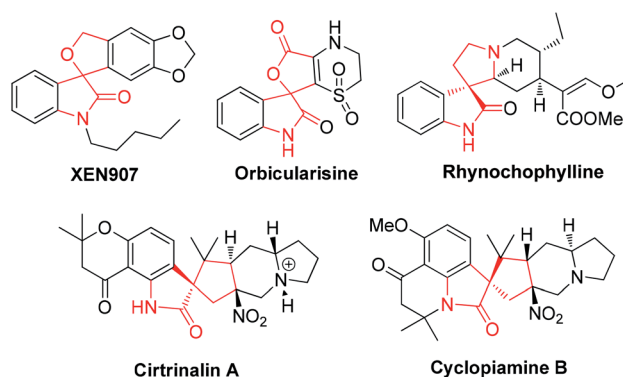


Fig. 1 Examples of biologically active spirocyclic oxindole scaffolds.

Yantai Key Laboratory of Nanomedicine & Advanced Preparations, Yantai Institute of Materia Medica, Shandong 264000, China. E-mail: [linchao46@163.com](mailto:linchao46@163.com); [qingteng51@163.com](mailto:qingteng51@163.com)

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra01086g



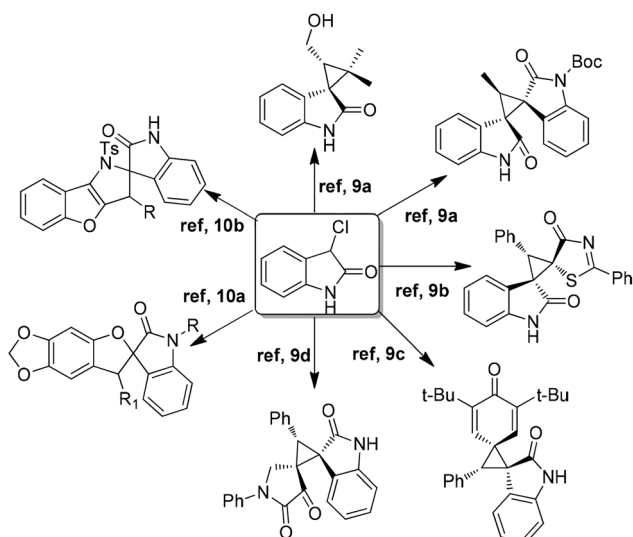


Fig. 2 Representation of the synthesis and applications of 3-chlorooxindoles.

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  $\text{CHCl}_3$ , 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

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.

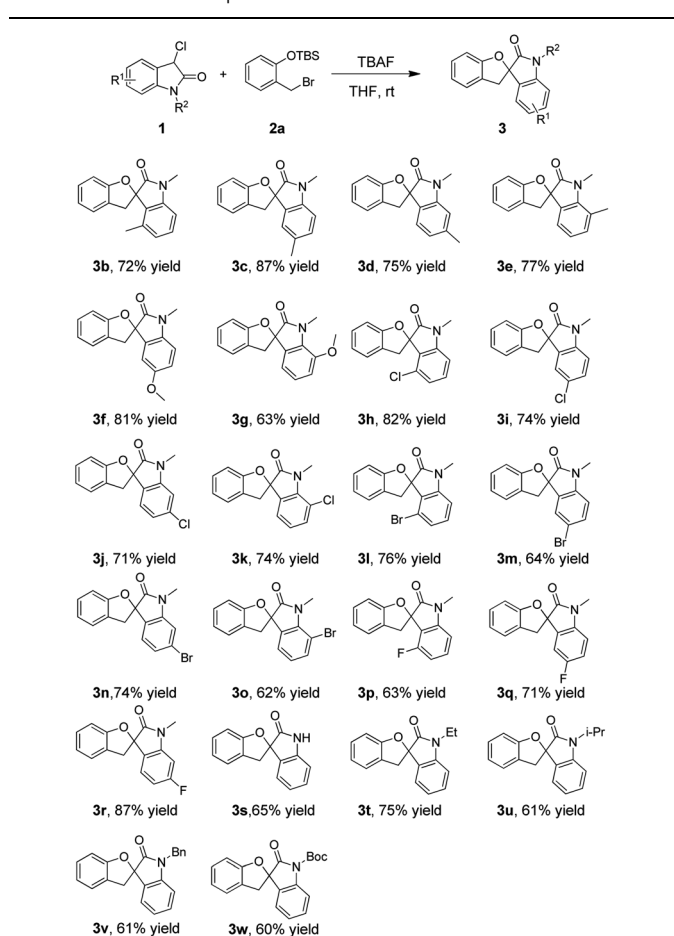
On the basis of above-mentioned results, a plausible mechanism for this formal [4 + 1] cycloaddition reaction is depicted in Scheme 1. Initially, the highly reactive *o*-QMs are generated

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	F <sup>-</sup> source	X	Y	Solvent	Temp (°C)	Yield <sup>b</sup>
1	TBAF <sup>c</sup>	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	$\text{CHCl}_3$	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

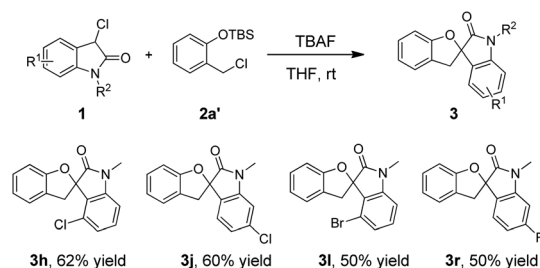
<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), solvent (3.0 mL), 6 h. <sup>b</sup> Isolated yield. <sup>c</sup> TBAF (1 M in THF solution).

Table 2 Substrate scope<sup>a,b</sup>

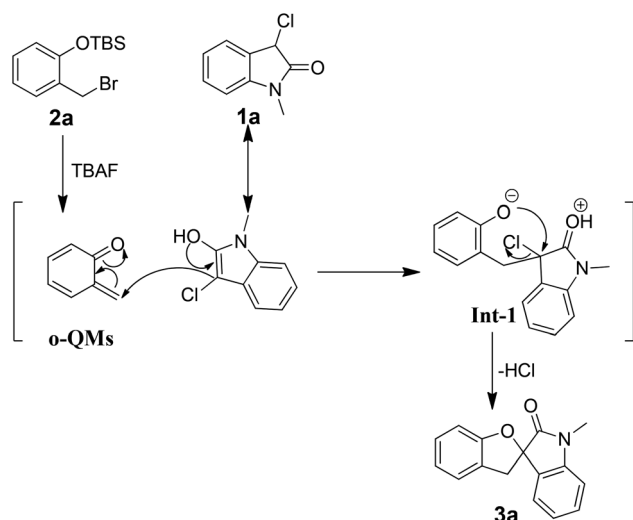


<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2a** (1.5 eq.), TBAF (4.0 eq.), THF (3.0 mL), 6 h. <sup>b</sup> Isolated yields.



Table 3 Substrate scope<sup>a,b</sup>

<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2a'** (1.5 eq.), TBAF (4.0 eq.), THF (3.0 mL), 6 h. <sup>b</sup> 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.

## Acknowledgements

The study was supported by the Science and Technology Innovation Development Planning Project of Yantai (2019MSGY128).

## Notes and references

- (a) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi and J. Zhou, *ACS Infect. Dis.*, 2016, **2**, 382; (b) T. L. Pavlovska, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Diversity*, 2016, **20**, 299; (c) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick and H. Waldmann, *Acc. Chem. Res.*, 2014, **47**, 1296; (d) E. F. Pimenta, A. M. Vita-Marques, A. Tininis, M. H. R. Selegim, L. D. Sette, K. Veloso, A. G. Ferreira, D. E. Williams, B. O. Patrick, D. S. Dalisay, R. J. Andersen and R. G. S. Berlinck, *J. Nat. Prod.*, 2010, **73**, 1821; (e) B. Zhang, W. Zheng, X. Wang, D. Sun and C. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 10435; (f) A. E. Fraley, K. C. Haatveit, Y. Ye, S. P. Kelly, S. A. Newmister, F. Yu, R. M. Williams, J. L. Smith, K. N. Houk and D. H. Sherman, *J. Am. Chem. Soc.*, 2020, **142**, 2244.
- S. Chowdhury, S.-F. Liu, J. A. Cadieux, T. Hsieh, M. Chafeev, S.-Y. Sun, Q. Jia, J.-Y. Sun, M. Wood, J. Langille, S. Sviridov, J.-M. Fu, Z.-H. Zhang, R. Chui, A. Wang, X. Cheng, J. Zhong, S. Hossain, K. Khakh, I. Rajlic, H. Verschoof, R. Kwan and W. Young, *Med. Chem. Res.*, 2013, **22**, 1825.
- (a) Y. M. Cao, F. F. Shen, F. T. Zhang and R. Wang, *Chem.-Eur. J.*, 2013, **19**, 1184; (b) L. Tian, X.-Q. Hu, Y.-H. Li and P.-F. Xu, *Chem. Commun.*, 2013, **49**, 7213; (c) D. Jiang, S. Dong, W. Tang, T. Lu and D. Du, *J. Org. Chem.*, 2015, **80**, 11593; (d) G.-J. Mei and F. Shi, *Chem. Commun.*, 2018, **54**, 6607; (e) X.-L. Jiang, S.-J. Liu, Y.-Q. Gu, G.-J. Mei and F. Shi, *Adv. Synth. Catal.*, 2017, **359**, 3341; (f) Q. Wan, L. Chen, S. Li, Q. Kang, Y. Yuan and Y. Du, *Org. Lett.*, 2020, **22**, 9539; (g) J. W. Wang, L. Zhao, Q. Rong, C. Lv, Y. Lu, X. Pan, L. Zhao and L. Hu, *Org. Lett.*, 2020, **22**, 5833; (h) X.-B. Huang, X.-J. Li, T.-T. Li, B. Chen, W.-D. Chu, L. He and Q.-Z. Liu, *Org. Lett.*, 2019, **21**, 1713.
- (a) W. Tan, X. Li, Y. X. Gong, M. D. Ge and F. Shi, *Chem. Commun.*, 2014, **50**, 15901; (b) Q. S. Sun, H. Zhu, Y. J. Chen, X. D. Yang, X. W. Sun and G. Q. Lin, *Angew. Chem., Int. Ed.*, 2015, **54**, 13253; (c) G. Zhan, M. L. Shi, Q. He, W. J. Lin, Q. Ouyang, W. Du and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 2147; (d) T. Fan, H. H. Zhang, C. Li, Y. Shen and F. Shi, *Adv. Synth. Catal.*, 2016, **358**, 2017; (e) Y. Chen, B. D. Cui, Y. Wang, W. Y. Han, N. W. Wan, M. Bai, W. C. Yuan and Y. Z. Chen, *J. Org. Chem.*, 2018, **83**, 10465; (f) K. Singh, S. Pramanik, T. A. Hamlin, B. Mondal, D. Das and J. Saha, *Chem. Commun.*, 2019, **55**, 7069; (g) Y. Lin, B. L. Zhao and D. M. Du, *J. Org. Chem.*, 2019, **84**, 10209; (h) R.-R. Liu, Y. Xu, R.-X. Liang, B. Xiang, H.-J. Xie, J.-R. Gao and Y.-X. Jia, *Org. Biomol. Chem.*, 2017, **15**, 2711; (i) B. Tan, N. R. Candeias and C. F. Barbas, *J. Am. Chem. Soc.*, 2011, **133**, 4672; (j) J. Zhang, C. Cheng, D. Wang and Z. Miao, *J. Org. Chem.*, 2017, **82**, 10121.
- For selected reviews on *o*-QMs, see: (a) N. J. Willis and C. D. Bray, *Chem.-Eur. J.*, 2012, **18**, 9160; (b) M. S. Singh, A. Nagaraju, N. Anand and S. Chowdhury, *RSC Adv.*, 2014, **4**, 55924; (c) T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210; (d) A. A. Jaworski and K. A. Scheidt, *J. Org.*



- Chem.*, 2016, **81**, 10145; (e) B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926; (f) S. Mukhopadhyay, C. Gharui and S. C. Pan, *Asian J. Org. Chem.*, 2019, **8**, 1970.
- 6 For selected examples of *o*-QMs in reactions, see: (a) P. Chen, K. Wang, W. Guo, X. Liu, Y. Liu and C. Li, *Angew. Chem., Int. Ed.*, 2017, **56**, 3689; (b) X. Gu, H. Yuan, J. Jiang, Y. Wu and W. J. Bai, *Org. Lett.*, 2018, **20**, 7229; (c) M. Sun, C. Ma, S. J. Zhou, S. F. Lou, J. Xiao, Y. Jiao and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 8703; (d) Y. You, T. T. Li, S. P. Yuan, K. X. Xie, Z. H. Wang, J. Q. Zhao, M. Q. Zhou and W. C. Yuan, *Chem. Commun.*, 2020, **56**, 439; (e) Z. Zhu, M. Odagi, N. Supantanapong, W. Xu, J. Saame, H.-U. Kirm, K. A. Abboud, I. Leito and D. Seidel, *J. Am. Chem. Soc.*, 2020, **142**, 15252; (f) F. Görlicke, S. Haseloff, M. Laue, M. Schneider, T. Brumme and C. Schneider, *J. Org. Chem.*, 2020, **85**, 11699.
- 7 (a) S. E. Rokita, J. H. Yang, P. Pande and W. A. Greenberg, *J. Org. Chem.*, 1997, **62**, 3010; (b) A. F. Barrero, J. F. Q. del Moral, M. M. Herrador, P. Arteaga, M. Corte's, J. Benites and A. Rosellón, *Tetrahedron*, 2006, **62**, 6012; (c) X. T. Lei, C.-H. Jiang, X. A. Wen, Q.-L. Xu and H. B. Sun, *RSC Adv.*, 2015, **5**, 14953.
- 8 (a) G. Bergonzini and P. Melchiorre, *Angew. Chem.*, 2012, **124**, 995; (b) A. Noole, I. Jarving, F. Werner, M. Lopp, A. Malkov and T. Kanger, *Org. Lett.*, 2012, **14**, 4922.
- 9 (a) A. Noole, M. Oseka, T. Pehk, M. Oeren, I. Jarving, M. R. J. Elsegood, A. V. Malkov, M. Lopp and T. Kanger, *Adv. Synth. Catal.*, 2013, **355**, 829; (b) Y.-X. Song and D.-M. Du, *Org. Biomol. Chem.*, 2019, **17**, 5375; (c) J.-R. Zhang, H.-S. Jin, J. Sun, J. Wang and L.-M. Zhao, *Eur. J. Org. Chem.*, 2020, **31**, 4988; (d) J.-B. Wen and D.-M. Du, *Org. Biomol. Chem.*, 2020, **18**, 1647.
- 10 (a) X. L. Jiang, S. J. Liu, Y. Q. Gu, G. J. Mei and F. Shi, *Adv. Synth. Catal.*, 2017, **359**, 3341; (b) C.-S. Wang, T.-Z. Li, Y.-C. Cheng, J. Zhou, G.-J. Mei and F. Shi, *J. Org. Chem.*, 2019, **84**, 3214.

