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Construction of Oxepino[3,2-*b*]indoles via [4+3] Annulation of 2-Ylideneoxindoles with Crotonate-Derived Sulfur Ylides

Xing-Hai Fei,[+a] Yong-Long Zhao,[+a,*] Fen-Fen Yang,[a] Xiang Guan,[a] Zong-Qin Li,[c] Da-Peng Wang,[b] Meng Zhou,[a] Yuan-Yong Yang,[a] and Bin He[a]

[a] State Key Laboratory of Functions and Applications of Medicinal Plants, School of Pharmacy, and Engineering Research Center for the Development and Application of Ethnic Medicine and TCM (Ministry of Education), Guizhou Medical University, Guiyang 550004, People's Republic of China
E-mail: zhaoyl05@126.com; zhaoyonglong@gmc.edu.cn

[b] Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, 550025, People's Republic of China

[c] Department of Neurology, Sichuan Mianyang 404 Hospital, Mianyang 621000, People's Republic of China

[+] These authors made equal contribution to this work.

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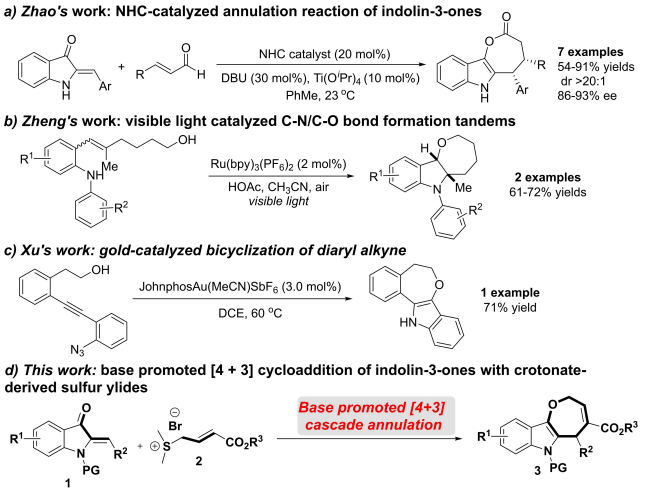
Abstract: A [4+3] annulation of 2-ylideneoxindoles with crotonate-derived sulfur ylides has been developed. A series of oxepino[3,2-*b*]indoles were prepared in moderate to excellent yields (62-93%) under mild conditions. Moreover, the synthetic oxepino[3,2-*b*] indoles can be further transformed into more complex cyclopropa[5,6]oxepino[3,2-*b*] indoles via a [2+1] cyclopropanation. In addition, the synthetic compounds show certain antiproliferative activity against K562 and MCF-7 cells, and its IC_{50} values for these two kinds of tumor cells up to 5.40±0.88 μM and 18.41±0.50 μM, respectively.

Keywords: 2-ylideneoxindoles; sulfur ylides; [4+3] annulation; oxepino[3,2-*b*]indoles

Indoles with a fused seven-membered ring at the C2- and C3-positions are prevalent in a wide range of natural products and biologically active molecules.[1–3] Because of its importance in structure and biological activity, these indole-fused seven-membered ring skeletons has drawn tremendous interest from both synthetic and medicinal chemists.[1,2] So far, although various synthetic methods have been developed for the construction of these indole-fused seven-membered ring skeletons,[1a,g,2,3] most of these established methods mainly focus on cyclohepta[*b*]indole skeletons[1a,2a–b] and indole-fused seven-membered nitrogen-heterocycle skeletons,[1g,2c–k] but the research on oxepino[3,2-*b*] indoles are generally lacking (Scheme 1).[3] In recently years, a few synthetic methods like NHC-catalyzed annulation reaction of indolin-3-ones with α,β-unsaturated aldehydes (Scheme 1a),[3d] visible light catalyzed diastereoselective oxidative C–N/C–O bond formation tandems (Scheme 1b)[3f] and gold-catalyzed bicyclization of diaryl alkyne (Scheme 1c)[3e] have been developed to construct oxepino[3,2-*b*] indole skeletons, however, these reported strategies usually require complex reaction system and have limited applications. Therefore, more efficient approaches for the construction of oxepino[3,2-*b*]indole skeletons is still highly desired.

Over the past decades, crotonate-derived sulfur ylides have been widely used as C1, C2 and C3 synthons in various cascade annulation reactions and has shown great potential in the synthesis of structurally diverse carbo- and heterocyclic skeletons.[2c,4] In particular, the formal [4+3] annulation involving crotonate-derived sulfur ylides has provided a powerful tool to construct highly functionalized seven-membered heterocycles.[4c,f,j] For example, by using above similar [4+3] cascade annulation strategies, the synthesis of thieno[3,2-*b*]oxepines,[4f] benzofuro[3,2-*b*] azepine[4c] and azepino[2,3-*b*]indole[4j] skeletons have been realized in recent years by Meng's, Huang's and Li's group, respectively. Despite these significant advances, it should be noted that the development of new cyclization domino reactions of crotonate-derived sulfur ylides with new substrates and its applications in the synthesis of important polycyclic skeletons remains to be developed. Based on our investigation of sulfur

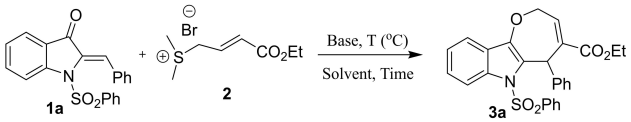


Scheme 1. Synthetic methods of oxepino[3,2-*b*]indoles.

ylide mediated cyclization domino reactions[2c,4] and indolin-3-one chemistry,[5] herein, we envisaged that the oxepino[3,2-*b*]indole skeletons **3** could be easily created via a base promoted [4 + 3] annulation reaction of crotonate-derived sulfur ylides **2** with 2-ylideneoxindoles **1** (Scheme 1d).

Initially, we chose pure (*Z*)-2-ylideneoxindole **1 a** and crotonate-derived sulfur ylide **2** as model substrates in the presence of Et_3N (1.5 equiv.) in MeCN at 25 °C (Table 1, entry 1). To our delight, the desired [4 + 3] annulation product **3 a** was obtained in 30% yield. To improve the yield and try to obtain other unprecedented annulation products,[4c,f,o] various organic and inorganic bases such as DABCO, K_2CO_3, K_3PO_4, NaOH, ^{t}BuOK and Cs_2CO_3 were also tested (Table 1, entry 1–7), and Cs_2CO_3 was founded to be the optimal choice (Table 1, entry 7). Interestingly, except for [4 + 3] annulation product **3 a**, no other annulation products were produced under the above-tested reaction conditions. Next, we evaluated the effect of solvents on this [4 + 3] cascade annulation

Table 1. Optimization of reaction conditions.[a]



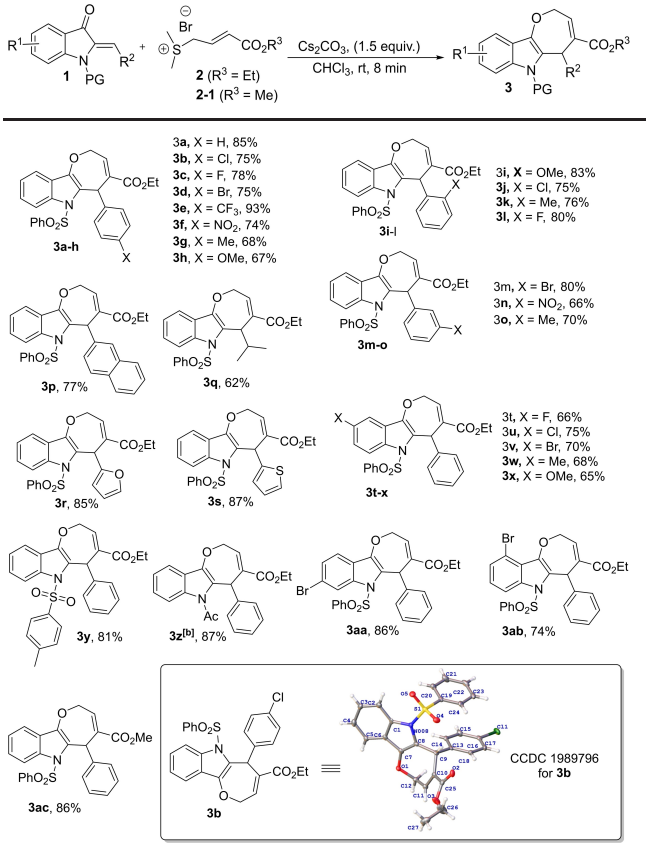
Entry	base (equiv.)	solvent	time (min)[e]	yield (%)[b]
1	Et_3N (1.5)	MeCN	20	30
2	DABCO (1.5)	MeCN	20	49
3	K_2CO_3 (1.5)	MeCN	120	45
4	K_3PO_4(1.5)	MeCN	20	49
5	NaOH (1.5)	MeCN	20	42
6	^{t}BuOK (1.5)	MeCN	240	32
7	Cs_2CO_3(1.5)	MeCN	20	55
8	Cs_2CO_3(1.5)	CH_2Cl_2	60	72
9	Cs_2CO_3(1.5)	THF	120	76
10	Cs_2CO_3(1.5)	$CHCl_3$	8	85
11	Cs_2CO_3(1.5)	toluene	300	11
12	Cs_2CO_3(1.5)	acetone	20	73
13[g]	Cs_2CO_3(1.5)	$CHCl_3$	90	61
14[h]	Cs_2CO_3(1.5)	$CHCl_3$	8	29
15	Cs_2CO_3(1.0)	$CHCl_3$	20	77
16	Cs_2CO_3(0.5)	$CHCl_3$	40	74
17[f]	Cs_2CO_3(1.5)	$CHCl_3$	300	51
18[c]	Cs_2CO_3(1.5)	$CHCl_3$	60	61
19[d]	Cs_2CO_3(1.5)	$CHCl_3$	40	72

[a] Reactions were performed with 0.10 mmol of **1 a**, 0.15 mmol of **2**, Cs_2CO_3 (1.50 equiv.) in 1.0 mL of the solvent for 8 min, reaction performed at 25 °C.
[b] The yields were isolated yields.
[c] **(*E*)-1 a**, 0.10 mmol.
[d] **(*Z*/*E*)-1 a**, 0.10 mmol, *Z*:*E* = 1:1.
[e] Reaction time was determined by TLC.
[f] 0.11 mmol of **2** was used.
[g] Reaction performed at 0 °C.
[h] Reaction performed at 50 °C.

reaction by screening solvents such as CH_2Cl_2, THF, $CHCl_3$, toluene, acetone and MeCN (Table 1, entry 7–12). Among the screened solvents, $CHCl_3$ was found to be the best solvent and the desired product **3 a** was obtained in 85% yield after only 8 minutes reaction time (Table 1, entry 10). Encouraged by these results, we then examined the effects of reaction temperatures (Table 1, entry 10, and 13–14) and the loading amounts of the Cs_2CO_3 and sulfur ylide **2** (Table 1, entry 10, and 15–17). Accordingly, the experimental results indicated that Cs_2CO_3 (1.5 equiv.), crotonate-derived sulfur ylide **2** (1.5 equiv.) and the solvent $CHCl_3$ at 25 °C are the optimal conditions for this annulation reaction (Table 1, entry 10). Under the optimal reaction conditions, we also examined the effects of *Z* or *E* configuration of 2-ylideneoxindole **1 a** for this annulation reaction, the results showed that longer reaction time are needed and the yield of desired product **3 a** are decreased when we used **(*E*)-1 a** or **(*Z*/*E*)-1 a** as a substrate (Table 1, entry 10 and 18–19). Therefore, we used pure (*Z*)-2-ylideneoxindoles **1** as the substrates in the later studies (Table 1, entry 10).

With the optimal reaction conditions established, we next investigated the substrate scope of this Cs_2CO_3 promoted [4 + 3] annulation reaction of crotonate-derived sulfur ylides **2** with (*Z*)-2-ylideneoxindoles **1** (Table 2). Generally, the desired annulation products **3 a–z** and **3 aa–3 ac** were obtained in 62–93% yields and the structure of **3 b** was unambiguously confirmed by single-crystal X-ray crystallography (Table 2).[6] Although some substrates (such as **1 ad–1 aj**) failed in synthesis (see the ESI), this substrate scope of this reaction is rather broad. For the substituents of aromatic ring R^2, both electron-withdrawing or electron-donating groups (**1 a–o**) at the different positions could be well tolerated in this [4 + 3] annulation reaction and the corresponding products **3 a–o** were obtained at 66–93% yields. Although slightly lower yields for products **3 g–h** and higher yield for product **3 e** were obtained, but the results of **3 a–o** revealed that this [4 + 3] annulation reaction was not obvious regular affected by steric hindrance and electronic effects of substituents at the aromatic ring R^2. In addition, the (*Z*)-2-ylideneoxindoles (**1 p–s**) bearing substituents such as 2-naphthyl, isopropyl and other heterocycles could also be well tolerated to yield corresponding products **3 p–s** albeit with 62% yield was obtained for isopropyl substituted product **3 q**. Next, we further investigated the effect of different R^1 substitutions of indolin-3-ones **1** on this annulation reaction, and the results showed that the presence of a halide (**1 t–v** and **1 aa–1 ab**), electron-withdrawing (**1 t**) or electron-donating (**1 w–x**) groups on the aromatic ring of indole-3-ones **1** could be also tolerated in this reaction and the desired products **3 t–x** and **3 aa–3 ab** were afforded with moderate yields (65–86%). Finally, N-tosyl or acetyl substituted indole-3-ones **1 y** or **1 z** have been also applied to this [4 + 3] annulation reaction, which gave the desired products **3 y–z** with good results (81–87% yields).

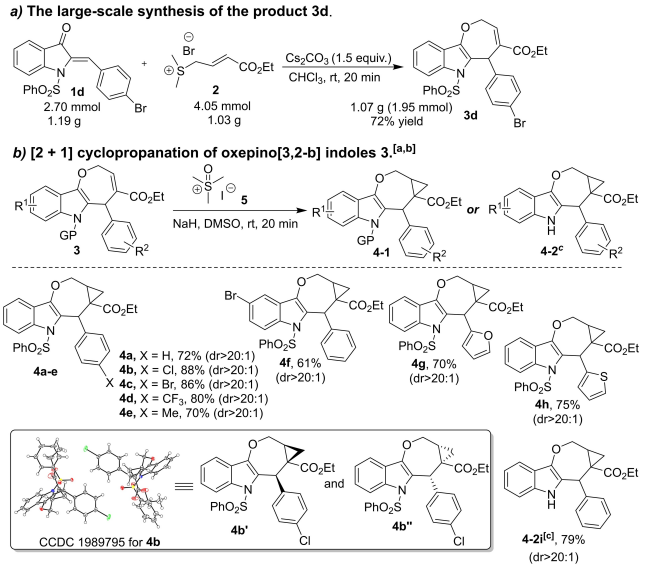
Table 2. Substrate scope of the [4 + 3] cascade annulation reaction.[a]



[a] Unless otherwise specified, all reactions were carried out with **1** (0.10 mmol, 1.0 equiv.), **2** (1.5 equiv.) and Cs_2CO_3 (1.5 equiv.) in 1.0 mL of the $CHCl_3$ for 8 min at 25 °C; the yields were isolated yields.

[b] Reaction time was 2 h.

To further investigate the potential application of this base promoted [4 + 3] cascade annulation strategy, the large-scale synthesis of oxepino[3,2-*b*] indole **3 d** and the further [2 + 1] cyclopropanation of the products **3** were also performed (Scheme 2). Firstly, the gram scale reaction of (*Z*)-2-ylideneoxindole **1 d** with crotonate-derived sulfur ylides **2** was conducted under the optimized conditions and the corresponding product **3 d** was obtained with 72% yield (Scheme 2a). To our delight, annulation products **3** could easily react with $(CH_3)_3SOI$ via a NaH promoted [2 + 1] cyclopropanation reaction to afford the cyclopropanation products **4 a–h** and **4–2 i** in 61–88% yields (dr > 20:1) and the relative configuration and structure of **4 b** was unambiguously confirmed by single-crystal X-ray crystallography (Scheme 2b).[6] To our surprise, the deacetylated product **4–2 i** could be obtained with 79%

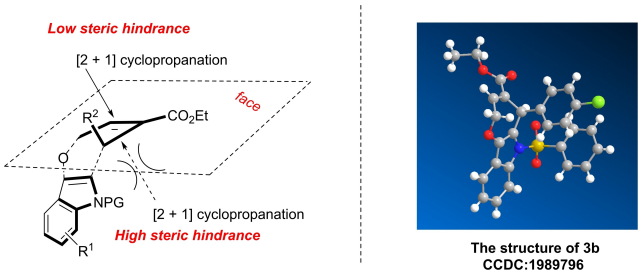


[a] Unless otherwise specified, all reactions were carried out with using **3** (0.10 mmol, 1.0 equiv.), **5** (1.1 equiv.) and NaH (60% dispersion on mineral oil, 1.2 equiv.) in 1.0 mL of the DMSO for 20 min (determined by TLC) at 25 °C; [b] The yields were isolated yields and dr values were determined by ^{1}H NMR analysis of the crude products **4**; [c] PG = Acetyl group.

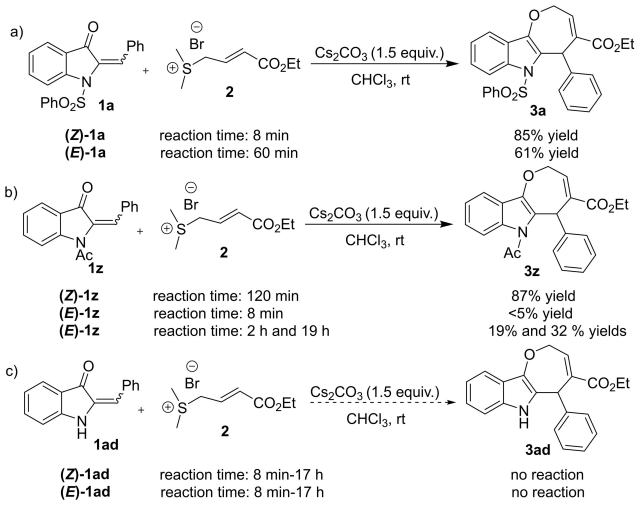
Scheme 2. The large-scale synthesis of the product **3 d** and [2 + 1] cyclopropanation of oxepino[3,2-*b*] indoles **3**.

yield (dr > 20:1) when *N*-acetyl substituted oxepino [3,2-*b*] indole **3 z** was used as substrate in above [2 + 1] cyclopropanation processes. In addition, a pilot screening of inhibitory activity of the synthetic compounds **3** and **4** against K562 and MCF-7 tumor cell lines were also performed (see the ESI). The results showed that the compound **3 r** and **4 d** had certain antiproliferative activity against K562 and MCF-7 cells (compound **3 r**: 72% and 85% inhibition at 50 μM, IC_{50} values are 8.24 ± 0.71 μM and 18.41 ± 0.50 μM; compound **4 d**: 88% and 95% inhibition at 50 μM, IC_{50} values are 5.40 ± 0.88 μM and 20.24 ± 0.10 μM).

The high diastereoselective results of [2 + 1] cyclopropanation reaction and relative configuration of cyclopropanation products **4** might be explained by the conformation of [4 + 3] annulation products **3**. As shown in Scheme 3, the R^2 groups and the indole residues as a larger steric part in annulation products **3** are in the opposite side of the carbon-carbon double bond face. Comparing with the *N*-protected indole residues, R^2 is less steric, so the [2 + 1] cyclopropanation reaction can easily occur on the side of the smaller steric hindrance R^2 group and obtained the corresponding cyclopropanation products **4** containing cyclopropane group and R^2 group which are positioned on the same side of seven membered ring structure. Next, we also investigated the effects of *Z*/*E* configurations and *N*-substituents of 2-ylideneoxindoles **1** for the base promoted [4 + 3] cascade annulation reactions (Scheme 4). Perhaps due to the steric hindrance effect



Scheme 3. The explaination of high diastereoselective [2 + 1] cyclopropanation reaction and relative configuration of cyclopropanation products **4**.

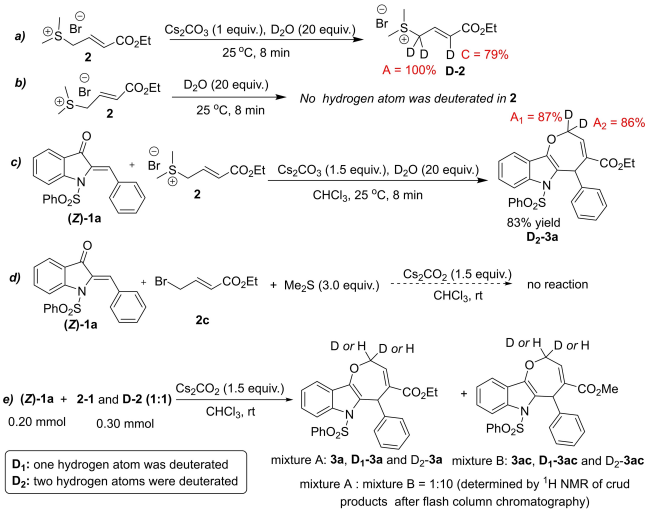


Scheme 4. The effects of *Z*/*E* configurations and *N*-substituents of 2-ylideneoxindole **1** for the base promoted [4 + 3] cascade annulation reactions.

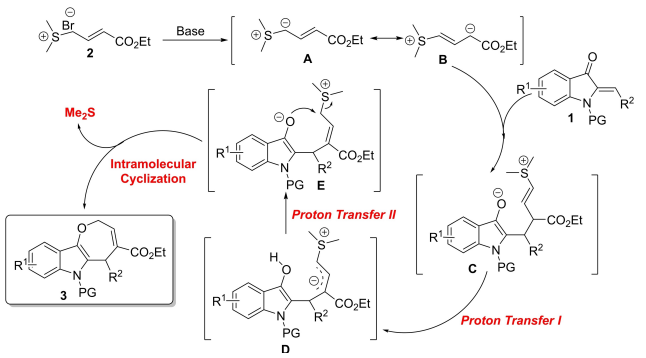
of *N*-substituents, the *Z*-configuration substrates (**1 a** and **1 z**) showed stronger reactivity than the *E*-configuration substrates (Scheme 4a-b). The experimental results also showed that the electronic effect of *N*-substituents of 2-ylideneoxindoles **1** has an obvious influence on this [4 + 3] cascade annulation reactions. In particular, there were no [4 + 3] cascade annulation reactions occurred for substrate **1 ad** bearing no electron-withdrawing substituents at the N1 position (Scheme 4c).

To better understand the mechanism of this [4 + 3] cascade annulation process, we performed the deuterium-labeling experiments and control experiments as shown in Scheme 3. In the presence of 20.0 equivalents of D_2O and 1.0 equivalents of Cs_2CO_3, 100% deuterium incorporation at the A-position and 79% deuterium incorporation at the C-position was observed in the ^{1}H NMR analysis (See the ESI) of sulfur ylide **D-2** (Scheme 3a). However, under the conditions of 20.0 equivalents of D_2O without Cs_2CO_3, no deuterated sulfur ylide **2** was observed (Scheme 3b). In

addition, under the standard procedure, we also performed the deuterium-labeling experiments for this [4+3] annulation reaction of crotonate-derived sulfur ylide **2** with (*Z*)-2-ylideneoxindole **1a** in the presence of 20.0 equivalents of D_2O, and 83% of **D-3a** was obtained with 87% deuterium incorporation at the A_1-position and 86% deuterium incorporation at the A_2-position (Scheme 3c). The above experimental results indicated that two kinds of carbanion allylic ylide resonance hybrids intermediates **A** or **B** (Scheme 6) could be generated from the sulfur ylide **2** and the base such as Cs_2CO_3 are very important for the formation of resonance hybrids intermediates **A** or **B**. More importantly, carbanion allylic ylide intermediates **B** might be the key active intermediate for this [4+3] cascade annulation reaction according to our experimental results of Scheme 5c. As shown in Scheme 5d, no reaction occurred when ethyl bromocrotonate **2c** and Me_2S were directly used in the reaction system to replace the corresponding sulfur ylide **2**. Finally, we also investigated this [4+3] annulation reaction of 2-ylideneoxindoles (*Z*)-**1a** with crotonate-derived sulfur ylides **2**–**1** and **D-2** (1:1) under the standard procedure. According to the ^{1}H NMR and HRMS analysis of crude reaction mixture, the determination of mixture A and mixture B (1: 10) revealed that this [4+3] annulation reaction may involve an intermolecular hydrogen transfer process (Scheme 5e, see the ESI).



Scheme 5. The deuterium-labeling experiments and control experiments for mechanism study.



Scheme 6. Proposed mechanism.

Based on our experimental results and previous related studies,[4c,f,g,h] a possible mechanism for this [4+3] annulation reactions was also proposed (Scheme 6). Firstly, deprotonation of crotonate-derived sulfur ylides **2** results in a carbanion allylic ylide intermediate **A** in the presence of a base (such as Cs_2CO_3). Carbanion allylic ylide intermediates **B** is formed by resonance of sulfur ylide intermediate **A**. Then, an intermolecular Michael addition involving α-selective addition of carbanion allylic ylide intermediate **B** to 2-ylideneoxindoles **1** via soft-soft interaction[4h] forms zwitterionic intermediate **C**. Next, the intermediate **C** easily transforms into zwitterionic intermediate **E** underwent two proton transfer processes (intermolecular proton transfer process may be involved). Finally, an intramolecular 7-exo-tet cyclization process of intermediate **E** was occurred to generate the products **3**.

In summary, we have developed a Cs_2CO_3 promoted [4+3] cascade annulation reaction of crotonate-derived sulfur ylides with 2-ylideneoxindoles. In the field of the indolin-3-one chemistry, this has become the first example of [4+3] cascade annulation reaction involving sulfur ylides as C3 synthons. Various oxepino[3,2-*b*]indoles were prepared in moderate to excellent yields (62-93%) via this strategy. Moreover, the synthetic oxepino[3,2-*b*] indoles **3** could be easily transformed into more complex cyclopropa[5,6] oxepino[3,2-*b*]indoles **4** via a [2+1] cyclopropanation and the synthetic compounds **3** and **4** show certain antiproliferative activity against K562 and MCF-7 cells. Further investigation and application of the oxepino[3,2-*b*] indoles and cyclopropa[5,6]oxepino [3,2-*b*]indoles are ongoing in our laboratories.

Experimental Section

General procedure for the 5,6-dihydro-2H-oxepino[3,2-*b*] indoles 3: To a solution of (*Z*)-2-ylideneoxindoles **1** (0.1 mmol) and sulfonium salt **2** (0.15 mmol, 1.5 equiv.) in $CHCl_3$ (1 mL) was added Cs_2CO_3 (0.15 mmol, 1.5 equiv.) under stirring at room temperature. After the required period of time (as judged by TLC analysis). The resulting solution was concentrated and directly purified by flash column chromatography (eluted with petroleum ether/EtOAc = 20/1 to 10/1) to afford the desired 5,6-dihydro-2H-oxepino[3,2-*b*]indoles **3**.

Synthetic transformations of product 3 to 4: To a solution of NaH (60% dispersion on mineral oil, 2.9 mg, 0.12 mmol) in dry DMSO (1 mL) was added $(CH_3)_3SOI$ (24.2 mg, 0.1 mmol). After the reaction mixture was stirred at room temperature for

15 min, 5,6-dihydro-2H-oxepino[3,2-*b*]indoles **3** (0.1 mmol) was dissolved in dry DMSO (0.5 mL) and added dropwise slowly. Then, the above reaction mixture was stirred for the required period of time (as judged by TLC analysis). The reaction mixture was extracted with EtOAc (3×50 mL) and then washed with brine. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo after filtration to give crude product. The crude product was directly purified by flash column chromatography (eluted with petroleum ether/EtOAc = 20/1 to 10/1) to give the desired product **4**.

Acknowledgements

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[6] See Supporting Information for details. CCDC 1989796 (**3 b**), 1989795 (**4 b**), contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data request/cif.

Construction of Oxepino[3,2-*b*]indoles via [4 + 3] Annulation of 2-Ylideneoxindoles with Crotonate-Derived Sulfur Ylides

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