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A rearrangement of saccharin-derived cyclic ketimines (SDCIs) and 3-chlorooxindoles leading to spiro-1,3-benzothiazine oxindoles†

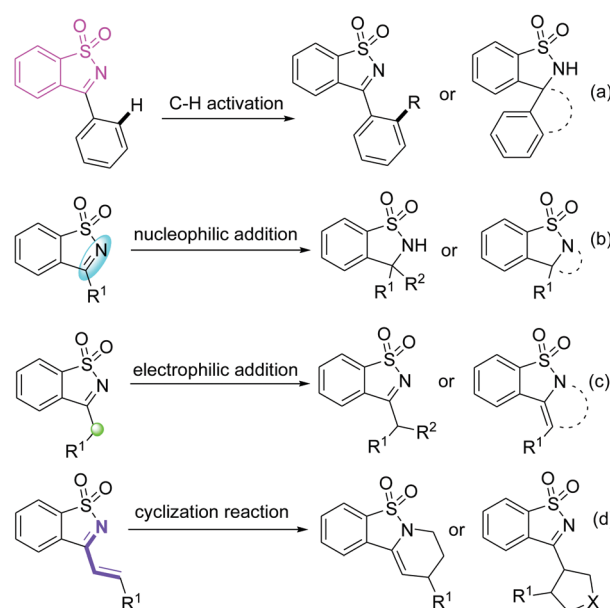
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An unusual rearrangement of saccharin-derived cyclic ketimines (SDCIs) and 3-chlorooxindoles has been developed to provide a series of spiro-1,3-benzothiazine oxindoles. The reaction features simple manipulations, short reaction times, mild reaction conditions and inexpensive reagents. It is the first example where SDCIs serve as a ring-opening reagent in organic synthesis.

Saccharin-derived cyclic ketimines (SDCIs) are a family of valuable and versatile building blocks in organic synthesis, and have been widely applied in various types of reactions for the synthesis of structurally diverse benzosultam derivatives.¹ Currently, SDCI-involved reactions can be mainly divided into four categories (Scheme 1): (a) C–H functionalizations, in which SDCIs act as a directing group to assist C–H cleavage of phenyl moiety at the 3-position;² (b) nucleophilic addition reactions, in which SDCIs participate as electrophiles reacting with various nucleophiles for the production of benzosultam-based adducts or cyclized products;³ (c) electrophilic addition reactions. In 3-alkyl substituted SDCIs, the α -proton is somewhat acidic due to the electron-withdrawing effect of the imine group. Thus, they can also be used as nucleophiles in organic synthesis;⁴ and (4) cycloaddition reactions of 3-vinyl substituted SDCIs serving as a 4- or 2-atom synthon for the construction of six- or five-membered heterocycles.⁵

In view of the importance of this building block in organic synthesis and based on our interest in the construction of spirocyclic compounds,⁶ we hope to open further its application to the construction of a spiro-aziridine oxindole compound with potential biological activities and thus devise a formal [2+1] cycloaddition reaction of SDCI with 3-chlorooxindole (Scheme 2a). To our surprise, this reaction failed to afford the anticipated spiro-aziridine oxindole product. Instead, we

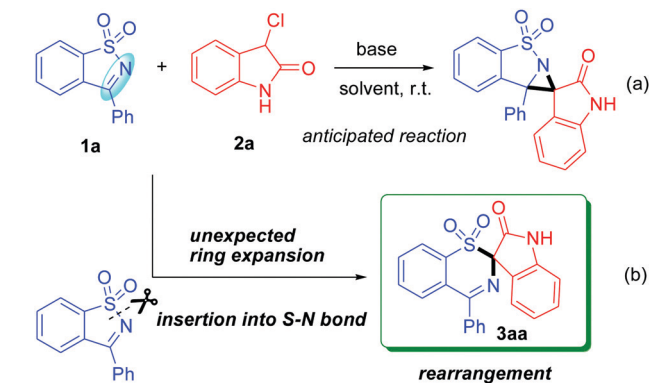
observed the formation of an unknown product in this reaction. Finally, the structure of the product was determined using single-crystal X-ray diffraction analysis and was identified as spiro-1,3-benzothiazine oxindole **3aa** (CCDC† 2098947; see the ESI†), which apparently arose from an unusual rearrangement. This rearrangement broke an $\text{ArS}(\text{O}_2)\text{--N}$ bond under very mild conditions in a short time, leading to an arylsulfonyl group migration from N to C involving a sulfonamide to sulfone rearrangement (Scheme 2b). This finding is very interesting because cleavage of the $\text{S}(\text{O}_2)\text{--N}$ bond generally requires relatively drastic conditions such as harsh reagents, long reaction times, and high reaction temperatures, as well as strongly acidic or basic conditions.⁷ Furthermore, exploration of the new role of SDCIs as a ring-opening reagent in a rearrangement reaction has not been previously reported.



Scheme 1 Reaction profiles of SDCIs.

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Scheme 2 The present work.

1,3-Benzothiazines are the core structural motifs of many biologically and pharmaceutically active molecules.⁸ Although there are several ways to prepare 1,3-benzothiazines,^{9–12} they are limited in structural diversification. For example, the chemistry on the construction of a spiro 1,3-benzothiazine framework is still underdeveloped.¹³ Spirocyclic scaffolds, especially spirooxindoles, are of great interest because they are not only useful intermediates in organic synthesis but offer great potential in drug discovery.¹⁴

Considering the above facts, we decided to develop this unexpected S–N bond insertion reaction as a general way to prepare spiro-1,3-benzothiazine oxindoles. Note that such a ring expansion/rearrangement not only enriches the chemistry of SDCIs but is also an extremely rare example of the construction of structurally interesting yet synthetically challenging spirocyclic systems that have potential synthetic usefulness and biological activities. In addition, although 3-chlorooxindoles have been widely used as one-atom synthons in organic synthesis, employing them in a rearrangement reaction is still unappreciated.

We chose to optimize the synthesis of **3aa** via the ring-expansion rearrangement using SDCI **1a** and 3-chlorooxindole **2a** as the model reaction, primarily examining the behavior of different bases and solvents on the reaction (Table 1). When the reaction was performed in THF at room temperature in the presence of DBU, the ring-expanded product **3aa** was formed in 73% yield within 30 min (entry 1). DBN gave a similar reaction yield with DBU (entry 2), whereas the use of other organic bases such as DABCO and Et₃N failed to improve the reaction yield even after 12 h (entries 3 and 4), presumably because of their lower basicity. Subsequent optimization with other bases revealed that Cs₂CO₃ was the most effective for the current reaction, affording the product **3aa** in 79% yield (entries 5–7). Further screenings showed that the reaction was not very sensitive to the solvent used and occurred smoothly in various solvents including ether solvents (e.g., DME and Et₂O), halogen solvents (e.g., CHCl₃), aprotic solvents (e.g., MeCN, DMF and DMSO), protic solvents (e.g., MeOH), and aromatic solvents (e.g., toluene) (entries 8–15). DME gave a better result and was chosen as the optimal solvent for the reaction (entry 8). Finally, the best result was achieved by conducting the reaction with a

Table 1 Optimization of the reaction conditions^a

Entry	Base	Solvent	Time	3aa ^b
1	DBU	THF	30 min	73
2	DBN	THF	30 min	72
3	DABCO	THF	12 h	37
4	Et ₃ N	THF	12 h	36
5	Na ₂ CO ₃	THF	30 min	74
6	Cs ₂ CO ₃	THF	30 min	79
7	^t BuOK	THF	30 min	74
8	Cs ₂ CO ₃	DME	30 min	87
9	Cs ₂ CO ₃	Et ₂ O	30 min	84
10	Cs ₂ CO ₃	CHCl ₃	30 min	81
11	Cs ₂ CO ₃	MeCN	30 min	79
12	Cs ₂ CO ₃	DMF	30 min	61
13	Cs ₂ CO ₃	DMSO	30 min	65
14	Cs ₂ CO ₃	MeOH	30 min	83
15	Cs ₂ CO ₃	Toluene	30 min	73
16 ^c	Cs ₂ CO ₃	DME	30 min	90

^a Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and a base in a solvent (1 mL) at room temperature.

^b Isolated yields. ^c **1a**:**2a** = 1:2. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DABCO, 1,4-diazabicyclo[2.2.2]octane; DME, 1,2-dimethoxyethane; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran.

1:2 ratio of **1a** and **2a** in the presence of Cs₂CO₃ in DME at room temperature (entry 16).

Various substituted SDCIs **1** and 3-chlorooxindoles **2** were subjected to the optimized reaction conditions. Compared with **1a** and **2a**, the substituted substrates required slightly longer times (1 h) for the rearrangement process. Table 2 shows that our ring-expansion rearrangement is compatible with functionalized and hindered R¹, R² and R³ groups. Generally, with respect to the 3-aryl substituted SDCIs **1**, both electron-donating and -withdrawing groups, regardless of the substitution patterns, on the arene moiety were well tolerated, giving the rearranged products in good to excellent yield (entries 1–7). When electron-rich substituents such as a methoxy group are present in the *ortho*, *meta* or *para* positions, the reactions proceeded smoothly, leading to the formation of products **3ba–3da** in 83–90% yield (entries 1–3). The bulky *t*-butyl substituent (**1e**) was well tolerated without any deleterious effect on the reaction efficacy being observed compared with a smaller methoxy group (**1d**) (entries 4 vs. 3). Substrates **1f** and **1g** bearing halogen substituents worked equally efficiently, affording **3fa** and **3ga** smoothly in 83% and 82% yields, respectively (entries 5 and 6). In addition to substrates with monosubstituted phenyl groups, those bearing disubstituted phenyl groups such as **1h** were also well tolerated, producing the corresponding product **3ha** in 86% yield (entry 7). The naphthalyl derived substrate **1i** also efficiently rearranged into the six-membered product **3ia** in 84% yield (entry 8). Next, the tolerance of 3-chlorooxindoles **2** was examined. 5-Methyl- and 6-methyl-3-chlorooxindoles (**2b** and **2c**) reacted very well in the reaction, affording the corresponding products **3ab** and **3ac** in 84% and 86% yields, respectively (entries 9 and 10). However, when the same substituent was moved to the 4-position, the desired reaction did not occur anymore (data not shown), and was probably due to steric hindrance. Substrates with a strong electron-donating methoxy group at the C5-position (**2d**) of the

Table 2 Substrate scope^a

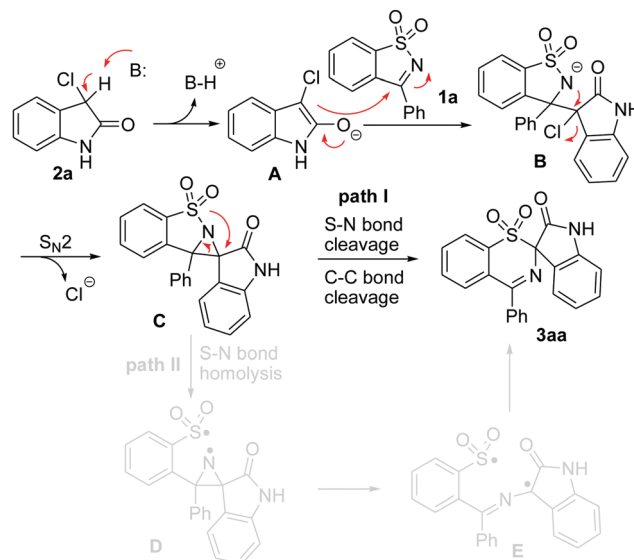
Entry	1	2	R ¹ /R ² /R ³	3	Yield ^b (%)
1	1b	2a	2-OMeC ₆ H ₄ /H/H	3ba	89
2	1c	2a	3-OMeC ₆ H ₄ /H/H	3ca	90
3	1d	2a	4-OMeC ₆ H ₄ /H/H	3da	83
4	1e	2a	4- ^t BuC ₆ H ₄ /H/H	3ea	86
5	1f	2a	3-FC ₆ H ₄ /H/H	3fa	83
6	1g	2a	4-ClC ₆ H ₄ /H/H	3ga	82
7	1h	2a	3,5-Me ₂ C ₆ H ₃ /H/H	3ha	86
8	1i	2a	2-Naphthyl/H/H	3ia	84
9	1a	2b	Ph/5-Me/H	3ab	84
10	1a	2c	Ph/6-Me/H	3ac	86
11	1a	2d	Ph/5-OMe/H	3ad	76
12	1a	2e	Ph/5-F/H	3ae	57
13	1a	2f	Ph/5-Cl/H	3af	56
14	1a	2g	Ph/5-Br/H	3ag	63
15	1a	2h	Ph/6-Cl/H	3ah	75
16	1a	2i	Ph/6-Br/H	3ai	70
17	1a	2j	Ph/H/Me	3aj	43
18	1a	2k	Ph/H/Boc	3ak	0
19	1c	2d	3-OMeC ₆ H ₄ /5-OMe/H	3cd	73
20	1e	2c	4- ^t BuC ₆ H ₄ /6-Me/H	3ec	87
21	1b	2h	2-OMeC ₆ H ₄ /6-Cl/H	3bh	86
22	1f	2b	3-FC ₆ H ₄ /5-Me/H	3fb	87
23	1f	2h	3-FC ₆ H ₄ /6-Cl/H	3fh	74

^a Reactions were carried out with **1** (0.1 mmol), **2** (0.2 mmol), and Cs₂CO₃ (0.2 mmol) in DME (1 mL) at room temperature for 1 h.

^b Isolated yields.

phenyl ring gave lower yields than their counterparts substituted with a methyl group (entries 11 vs. 9). For 3-chlorooxindoles **2** with halo-substituents at the C5-position, such as **2e–2g**, the reaction efficiency was decreased to afford the products **3ae–3ag** in 56–63% yields, which was due to the low conversion of **1a** and the concomitant formation of unidentified byproducts (entries 12–14). For the C6 halogenated substrates (**2h** and **2i**), good reaction yields and clean reactions were retained (entries 15 and 16). When a methyl group was introduced to the nitrogen atom of 3-chlorooxindoles, the yield of the rearranged product **3aj** decreased significantly (entry 17). No reaction occurred when using a Boc group in place of the methyl group on the nitrogen atom (entry 18). Finally, various substituted SDCIs **1** and 3-chlorooxindoles **2** were subjected to the above optimal reaction conditions. As expected, when there were substituents on both phenyl rings, the reactions could also afford the sulfonative products **3cd**, **3ec**, **3bh**, **3fb**, and **3fh** in good yields, irrespective of the electronic property and substitution pattern of the substituent (entries 19–23). These results highlighted the broad substrate scope of the Cs₂CO₃-mediated new rearrangement reactions of SDCIs and 3-chlorooxindoles.

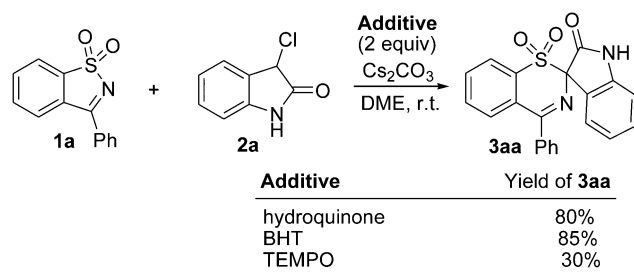
For the formation of the rearranged product **3**, we put forward two plausible pathways as shown in Scheme 3. Both pathway I and pathway II are initiated by the nucleophilic attack of the initially formed enolate **A**¹⁵ on the C=N bond of



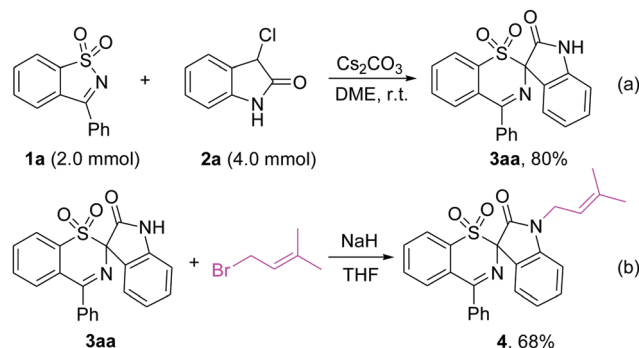
Scheme 3 Two potential mechanistic pathways.

1 to generate a nitrogen anion **B**, which is further transformed into the aziridine **C** via an intramolecular S_N2-type nucleophilic substitution.¹⁶ Pathway I involves the 1,2-shift of an arylsulfonyl group from a N atom to a C atom with a concomitant S–N cleavage followed by rapid cleavage of the C–C bond to yield the rearranged sulfone **3**. Another possibility is that intermediate **C** undergoes the homolysis of the S–N bond to afford biradical **D**, which would undergo aziridine ring opening to form a more stable carbon-center radical **E**.¹⁷ Finally, product **3** is produced by bond formation between the S and C radical species (pathway II).

To understand the above proposed mechanisms, control experiments of **1a** with **2a** were conducted in the presence of a radical-trapping reagent, such as hydroquinone, 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (Scheme 4). It was observed that the addition of hydroquinone or BHT did not inhibit the reaction and **3aa** was obtained in an 80% or 85% yield, respectively. When TEMPO was added to the reaction, **3aa** was obtained in a ca. 30% yield. These results indicate that the radical process might not be involved in the present reaction. On the basis of these observations, we consider that it is possible that the reaction proceeded via the former mechanism.



Scheme 4 Control experiments.



Scheme 5 Scale-up synthesis and further transformation of 3aa.

Performing the rearrangement reaction on a larger scale using 2.0 mmol of **1a** and 4.0 mmol of **2a** as substrates gave **3aa** in 80% yield (Scheme 5a). When **3aa** was treated with prenol bromide in the presence of NaH in THF, the prenylated indole **4** was obtained in 68% yield, which is a privileged structural unit present in many *N*-prenylindole alkaloids such as the fumitremorgin B and flustramine families of alkaloids (Scheme 5b).¹⁸

In conclusion, an unusual rearrangement reaction between SDCIs and 3-chlorooxindoles under mild conditions has been developed. This reaction occurred *via* a S–N bond insertion process followed by an arylsulfonyl group transfer, thus leading to a novel reaction mode involving SDCIs and the construction of novel and structurally interesting spirocyclic compounds. Moreover, this work uncovered the hidden potential of SDCIs in organic synthesis, which would be helpful for the further development of new reactions with SDCIs.

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Conflicts of interest

There are no conflicts to declare.

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