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Highly Efficient and Stereoselective Construction of Dispiro-[oxazolidine-2-thione]bisoxindoles and Dispiro [imidazolidine-2-thione]bisoxindoles

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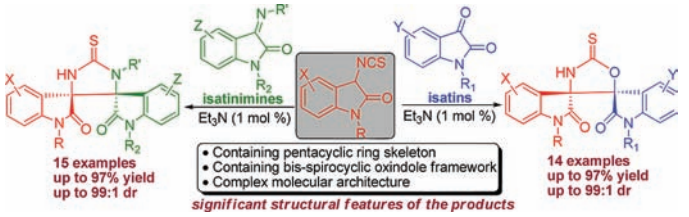
ABSTRACT



An efficient and stereoselective reaction between 3-isothiocyanato oxindoles and isatins/isatinimines has been developed to afford structurally diverse dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazolidine-2-thione]bisoxindoles in excellent results under mild conditions. The potential of asymmetric induction by means of a chiral auxiliary was explored. The isomers are separable, and products could be isolated as single diastereomers by column chromatography. Further synthetic transformations of the reaction product were also successfully realized.

The development of efficient methods to construct spiro compounds has been a topic of great relevance in organic synthesis due to the pronounced biological activities of this class of compounds.[1] In particular, the spirocyclic oxindoles have emerged as attractive synthetic targets because of their prevalence in numerous natural and unnatural products.[2] A variety of synthetic strategies have been developed to access analogous compounds possessing the spirocyclic oxindole skeleton.[2,3] Notably, these diverse spirocyclic oxindoles are characterized by a spiro ring fusion at the C3 position of the oxindole core with varied heterocycle motifs (Figure 1). In addition, a report has it that sharing of the oxindole C3 atom in the construction of

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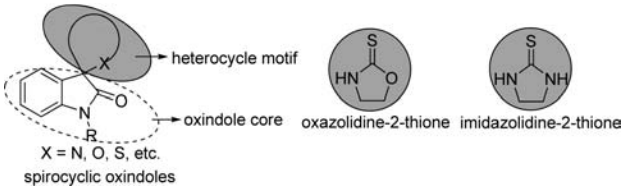
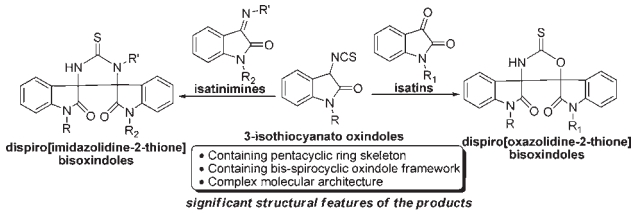


Figure 1. Fusing the oxindole core with different heterocycle motifs for the construction of spirocyclic oxindoles.

spirocyclic oxindole compounds can enhance biological activity.[4] Thus, the fusion of oxindole motifs with different heterocycles for the formation of structurally diverse spirocyclic oxindoles has attracted significant attention from organic chemists.[2,5] More importantly, these fused-heterocycle compounds seem to be promising candidates for biological responses since they incorporate both oxindoles and other heterocyclic moieties simultaneously. However, a careful survey of the relevant literature reveals that only we and Wang et al. independently reported different methods for fusing an oxazolidine-2-thione motif (Figure 1) into the oxindole C3 position to deliver spiro[oxazolidine-2-thione-oxindoles].[6,7] Nevertheless, the realization of employing an imidazolidine-2-thione (Figure 1) moiety for generating the corresponding spiro[imidazolidine-2-thione-oxindoles] remains elusive.

We recently synthesized a series of 3-isothiocyanato oxindoles and successfully used them as nucleophiles for asymmetric synthesis of a range of enantioenriched spirocyclic oxindoles bearing two highly congested contiguous tetrasubstituted carbon stereocenters.[6] Based on this achievement and our recent successes in the development

Scheme 1. Our Strategy for the Construction of Two New Classes of Spirocyclic Oxindoles



of new methodologies for the construction of diverse 3,3′-disubstituted oxindole derivatives,[6,8] we were further intrigued by the reactions of 3-isothiocyanato oxindoles with isatins and isatinimines (Scheme 1). As illustrated in Scheme 1, the reactions will afford dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazolidine-2-thione]-bisoxindoles, which are two new classes of spirocyclic oxindoles. It is noteworthy that the significant structural features of these spirocyclic oxindole products include pentacyclic ring skeleton, bis-spirocyclic oxindole framework, and complex molecular architecture. Undoubtedly, these spirocyclic oxindole compounds may provide promising candidates for chemical biology and drug discovery, due to the fact that some spirocyclic bisindoles have recently emerged as promising scaffolds for anticancer activity.[9] Herein, we wish to report our preliminary efforts on the subject regarding the development of an efficient method for the construction of two classes of novel spirocyclic oxindoles.

Initially, the reaction of 3-isothiocyanato oxindole **1a** and istain (**2a**) in dichloromethane (DCM)[10] at rt was selected as the model reaction (Table 1). The blank reaction of the model reaction afforded the desired product **4aa** in 80% yield in 99:1 dr after 240 min (Table 1, entry 1). From this reaction, we were aware that the reaction easily took place and showed high reactivity. Despite this, we further examined several bases to further improve the reaction. We were pleased to find that the reaction rapidly went to completion with 20 mol % Et_3N to give **4aa** in 91% yield with 99:1 dr only in 2 min (Table 1, entry 3). Based on the reactivity and diastereoselectivity, the catalysis of Et_3N was significantly better than that of DABCO, Na_2CO_3, DIPEA, and DIPA (Table 1, entry 2 vs 4−6). Subsequently, with Et_3N as the catalyst, the different catalyst loadings were surveyed (Table 1, entries 7−9). Finally, it was observed that the reaction was able to proceed to completion in 2 min even with 1 mol % Et_3N and afford product **4aa** in 90% yield with 92:8 dr (Table 1, entry 9).

Under the optimized conditions the reactions of 3-isothiocyanato oxindoles and isatins were investigated. As

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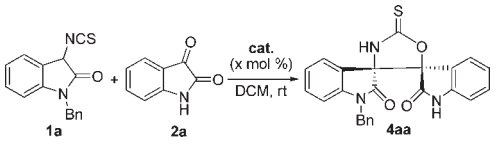
(10) Allowing for the solubility of the substrates and the convenience of operation, dichloromethane was screened out from THF, DMSO, DMF, H_2O, and toluene as the perfect solvent in this work.

Table 1. Optimization of the Reaction of 3-Isothiocyanato Oxindole **1a** and **2a**[a]



entry	cat.	x	time	dr[b]	yield (%)[c]
1	–	–	240 min	99:1	80
2	DABCO	20	90 min	91:9	93
3	Et_3N	20	2 min	99:1	91
4	Na_2CO_3	20	240 min	99:1	92
5	DIPEA	20	2 min	92:8	93
6	DIPA	20	2 min	75:25	94
7	Et_3N	10	2 min	94:6	90
8	Et_3N	5	2 min	92:8	92
9	Et_3N	1	2 min	92:8	90

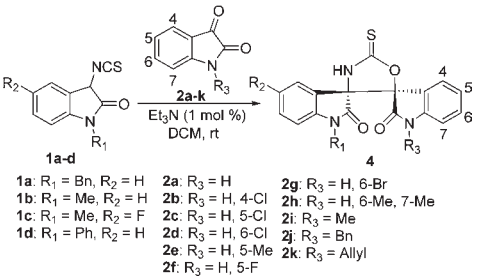
[a] The reactions were carried out with **1a** (0.04 mmol) and **2a** (0.04 mmol) with specified catalyst loading in DCM (1.0 mL) at rt. [b] Determined by ^1H NMR analysis of the product after purification via flash chromatography. [c] Isolated yield. DABCO = 1,4-diazabicyclo-[2.2.2]octane, DIPEA = diisopropylethylamine, DIPA = diisopropylamine.

summarized in Table 2, it was found that 3-isothiocyanato oxindoles **1a**–**d** reacted smoothly with a variety of isatins **2a**–**k** to generate the structurally diverse dispiro-[oxazolidine-2-thione]bisoxindoles **4ab**–**da** only in the presence of 1 mol % Et_3N. In all cases, high yields ranging from 80 to 97% were achieved under the optimized conditions, and the rate of the reactions were very fast. Of particular interest was that excellent diastereoselectivity, as high as 99:1, could be obtained for most of the cases except **4ab** and **4ae** (Table 2, entries 1 and 4). It was observed that product **4ab** could be obtained in 84% yield only with 50:50 dr; this may be attributed to the steric hindrance of the 4-chloro-substituted isatin **2b** (Table 2, entry 1). *N*-Methyl-3-isothiocyanato oxindole **1b** reacting with isatin **2a** needs only 5 min for full conversion and affords 95% of product **4ba** with 99:1 dr (Table 2, entry 11). Additionally, X-ray crystal structure analysis of the major diastereoisomer of product **4af** confirmed the exact structure and the relative stereochemistry as the *trans* configuration.[11] Furthermore, a large scale experiment was performed to test the potential practicality of this process (Table 2, entry 14). In the presence of 1 mol % Et_3N for only 60 min, product **4aa** was isolated in 84% yield with 99:1 dr.

Having established a general scope with respect to the reaction between 3-isothiocyanato oxindoles and isatins (Table 2), we next investigated a similar reaction with various isatinimines **3a**–**i** in place of isatins. As shown in Table 3, under the optimized reaction conditions from Table 1, the reactions between 3-isothiocyanato oxindoles and an array of *N*-PMP isatinimines occurred smoothly to provide the corresponding spirocyclic oxindoles with high reactivity (2–44 min), in moderate to excellent diastereoselectivity

(11) See Supporting Information for the CIF files of **4af** and **5aa**.

Table 2. Substrate Scope Studies for the Reaction of 3-Isothiocyanato Oxindoles and Isatins[a]



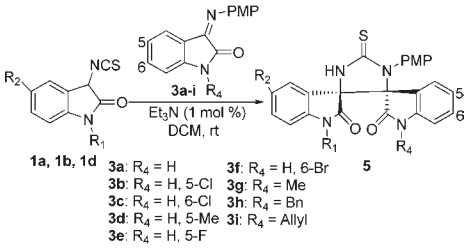
entry	1	2	4	time	dr[b]	yield (%)[c]
1	**1a**	**2b**	**4ab**	120 min	50:50	84
2	**1a**	**2c**	**4ac**	60 min	99:1	87
3	**1a**	**2d**	**4ad**	10 min	99:1	93
4	**1a**	**2e**	**4ae**	20 min	92:8	92
5	**1a**	**2f**	**4af**	20 min	99:1	87
6	**1a**	**2g**	**4ag**	35 min	99:1	80
7	**1a**	**2h**	**4ah**	40 min	99:1	91
8	**1a**	**2i**	**4ai**	40 min	99:1	97
9	**1a**	**2j**	**4aj**	40 min	99:1	95
10	**1a**	**2k**	**4ak**	20 min	99:1	92
11	**1b**	**2a**	**4ba**	5 min	99:1	95
12	**1c**	**2a**	**4ca**	60 min	99:1	92
13	**1d**	**2a**	**4da**	50 min	99:1	91
14	**1a**	**2a**	**4aa**	60 min	99:1	84[d]

[a] All reactions were performed with **1** (0.11 mmol) and **2** (0.11 mmol) in the presence of 1 mol % Et_3N in DCM (3.0 mL) at rt. [b] Determined by ^1H NMR analysis of the product after purification via flash chromatography. [c] Isolated yield. [d] Large scale experiment: **1a** (2.9 mmol, 0.8 g), **2a** (2.9 mmol, 0.42 g) with 1 mol % Et_3N in DCM (80 mL) at rt for 60 min.

(57:43–99:1) and high yield (84–97%). Notably, a class of novel structural dispiro[imidazolidine-2-thione]bisoxindoles **5aa**–**da** could be readily constructed for the first time with this protocol. It was noteworthy that product **5ag** could be obtained in 97% yield with 99:1 dr only after 2 min (Table 3, entry 7). Nevertheless, we also found that a variety of functional groups at different positions of isatinimines (5-, 6-, and *N*-1 positions) were tolerated well under the conditions. The structure and relative stereochemistry (*trans*-fused) for the major diastereoisomer were fortunately determined by using the X-ray crystallography of **5aa**.[11]

Prompted by the above results, we attempted to further employ isatinimines **6a** and **6b**, containing an *O*-TBDMS (*R*)-phenylglycinol chiral auxiliary, as substrates for exploring the potential of asymmetric induction (Table 4). To our delight, we found that the reaction generally exhibited high efficiency. The starting materials were smoothly consumed after 3 h in the presence of 1 mol % Et_3N at rt, and the desired more complex spirocyclic oxindole products, containing three stereogenic centers, were able to be readily obtained in highly combined yields (Table 4). Interestingly, in the cases for the generation of **7db**, **7ca**, and **7da**, any one of the diastereomers formed in the reaction could be easily obtained by column chromatography, thus giving access to the corresponding optically active isomeric products (Table 4, entries 2–4). Meanwhile, during the preparation

Table 3. Substrate Scope Studies for the Reaction of 3-Isothiocyanato Oxindoles and Isatinimines[a]



entry	1	3	5	time	dr[b]	yield (%)[c]
1	**1a**	**2a**	**5aa**	20 min	86:14	87
2	**1a**	**2b**	**5ab**	26 min	80:20	84
3	**1a**	**2c**	**5ac**	20 min	57:43	95
4	**1a**	**2d**	**5ad**	35 min	91:9	91
5	**1a**	**2e**	**5ae**	30 min	83:17	95
6	**1a**	**2f**	**5af**	44 min	83:17	90
7	**1a**	**2g**	**5ag**	2 min	99:1	97
8	**1a**	**2h**	**5ah**	30 min	99:1	90
9	**1a**	**2i**	**5ai**	20 min	94:6	90
10	**1b**	**2a**	**5ba**	12 min	99:1	91
11	**1d**	**2a**	**5da**	20 min	99:1	87

[a] All reactions were performed with **1** (0.11 mmol) and **3** (0.11 mmol) in the presence of 1 mol % Et_3N in DCM (3.0 mL) at rt. [b] Determined by ^1H NMR analysis of the product after purification via flash chromatography. [c] Isolated yield. PMP = *p*-methoxyphenyl.

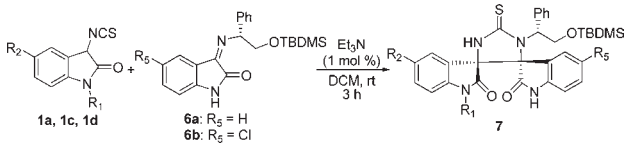
of **7aa**, we separated two products: one was an optically active isomer in 67% yield, and the other was a mixture of two diastereomers in 25% yield with 23:4 dr (Table 4, entry 1).

Finally, versatile transformations of **4aa** into other structurally diverse oxindole derivatives **8**–**10** were successfully realized.[12] As shown in Scheme 2, product **4aa** could be readily transformed to compound **8** by reacting with iodomethane in acetone at rt in 96% yield and 99:1 dr. In addition, protection of the two NH groups was carried out by treatment of **4aa** with *tert*-butyloxycarbonyl anhydride in the presence of 5 mol % 4-dimethylamiopryidine (DMAP) in CH_2Cl_2, and then, the reaction mixture was directly subjected to an oxidation reaction with a solution of 30% aqueouos H_2O_2 and 88% aqueouos formic acid in CH_2Cl_2, giving compound **9** with 99:1 dr in 87% yield in two steps. Significantly, the hydrolysis of **9** with LiOH in the mixture of dioxane and THF smoothly afforded product **10** in 90% yield with 99:1 dr.

In conclusion, we have developed a method for highly efficient and diastereoselective construction of structurally diverse dispiro[oxazolidine-2-thione]bisoxindoles and dispiro[imidazolidine-2-thione]bisoxindoles by the reaction of 3-isothiocyanato oxindoles with isatins and isatinimines. The reactions occurred readily only in the presence of 1 mol % Et_3N under mild reaction conditions, affording the desired products in excellent yields (up to 97%) and diastereoselectivities (up to 99:1). Particularly valuable

(12) Details of the transformation procedures are provided in the Supporting Information.

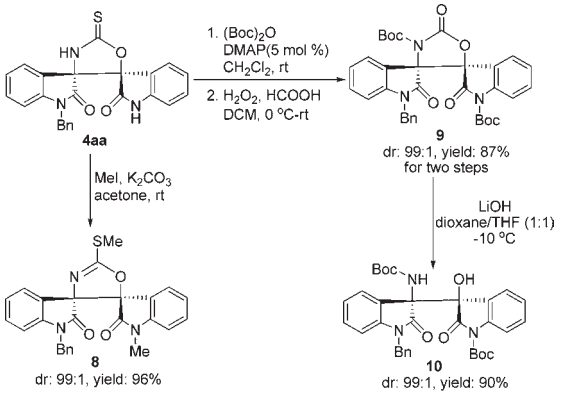
Table 4. Exploration for the Potential of Asymmetric Induction[a]



entry	1	6	7	dr[b]	yield (%)[c]
1	**1a**	**6a**	**7aa**	23:4:73:0	25[d]+67 = 92
2	**1d**	**6b**	**7db**	67:33:0:0	60+30 = 90
3	**1c**	**6a**	**7ca**	50:50:0:0	46+46 = 92
4	**1d**	**6a**	**7da**	75:6:19:0	67+6+17 = 90

[a] Unless otherwise specified, the reactions were carried out with **1** (0.11 mmol) and **6** (0.11 mmol) in the presence of 1 mol % Et_3N in DCM (3.0 mL) at rt. [b] Based on isolated yield. [c] Isolated yield. [d] Isolated yield for the mixture of two diastereomers. TBDMS = *tert*-butyldimethylsilyl.

Scheme 2. Transformations of the Product **4aa** to Other Oxindole Derivatives



features of these spirocyclic oxindole products include a pentacyclic ring skeleton, bis-spirocyclic oxindole framework, and complex molecular architecture. Moreover, by means of a chiral auxiliary for exploring the potential of asymmetric induction, it was found that the isomers are separable and products could be easily isolated as single diastereomers by column chromatography. Finally, synthetic transformations of the reaction product were also successfully realized. Biological evaluation and efforts to make the reaction enantioselective are ongoing.

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Supporting Information Available. Experimental details, characterization data for new compounds, X-ray crystal structure, and the CIF files of **4af** and **5aa**. This material is available free of charge via the Internet at http://pubs.acs.org.