Concise Synthesis of Thiazolo[4,5-*b*]indoles via Ring Switch /Cyclization Sequences

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Abstract: The unexpected reactions of indoline hemiaminals affords 2,5-diaryl-4-hydroxythiazolines through a thioamidation/ring switch sequence. The key to success of this transformation is to use a thioamide as a thiazoline precursor under transient tautomeric control. This transformation features mild reaction conditions and good yields with broad functional group tolerance (17 examples, up to 99% yield). Further transformations of the thiazolines provide a direct entry to dihydrothiazolo[4,5-*b*]indoles and thiazolo[4,5-*b*]indoles.

Introduction

Thiazoloindoles,[1] such as isothiazolo[5,4-*b*]indole alkaloids brassilexin and sinalexin,[2] thiazolo[3,2-*a*]indole alkaloid brassicanal B,[3] thiazolo[3,4-*a*]indoles,[4] thiazolo[5,4-*e*]indoles,[5] thiazolo[5,4-*b*]indoles,[6] and thiazolo[4,5-*b*]indoles,[7] are important thiazole-fused indole derivatives present in a large number of naturally occurring and artificial heterocycles with significant biological activities (Figure 1).

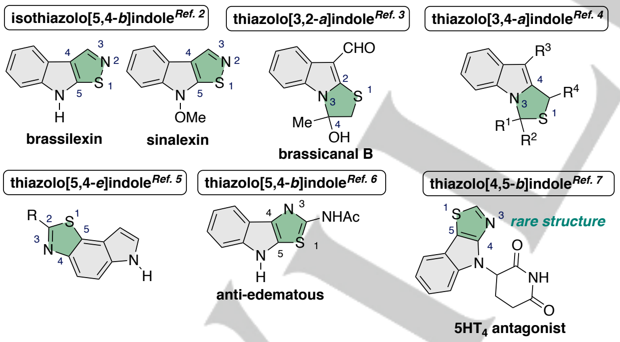
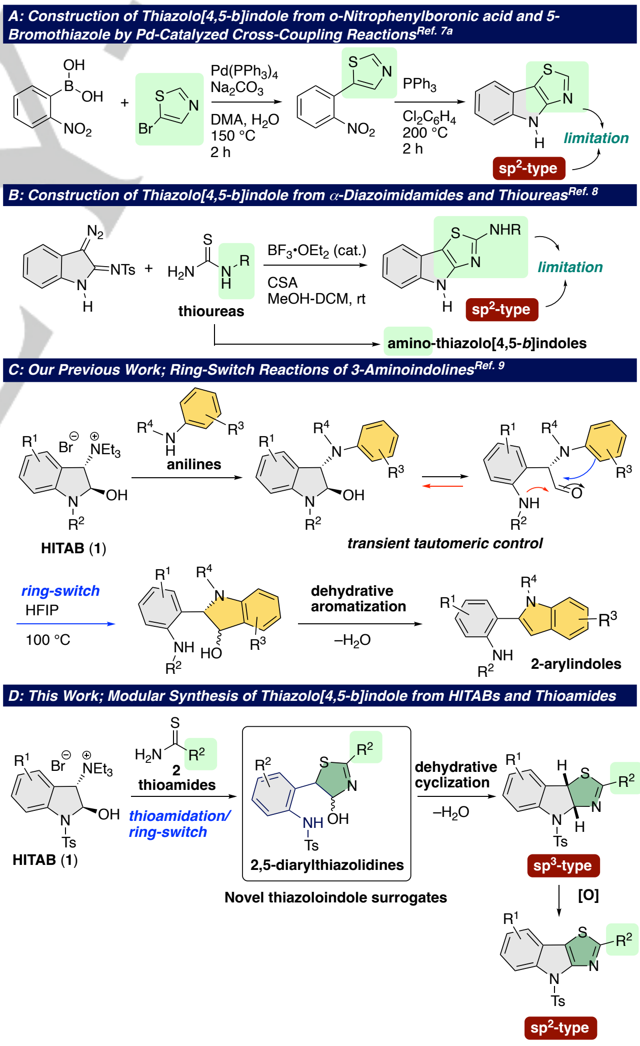


Figure 1. Reported thiazoloindoles.

Therefore, the development of diverse protocol for their synthesis has attracted much attention.[1] However, compared with other thiazoloindoles, the thiazolo[4,5-*b*]indoles remain scare. In 2020, Zhang and co-workers reported the first construction of thiazolo[4,5-*b*]indoles through a Suzuki-Miyaura cross coupling reaction of 5-bromothiazole with 2-nitrophenyl boronic acid (sp^2-type: Scheme 1A).[7] In 2023, Muthusamy and co-workers reported a BF_3•OEt_2-catalyzed synthesis of aminothiazolo[4,5-*b*]indoles from α-diazoimidamides and thioureas (sp^2-type: Scheme 1B).[8] The use of thioureas was necessary to promote the nucleophilic attack at the C3-position of the indole ring, and successive cyclization gave amino-substituted thiazolo[4,5-*b*]indoles. However, these reactions provide the sp^2-type thiazolo[4,5-*b*]indoles. To the best of our knowledge, the modular synthesis of sp^2- or sp^3-type thiazolo[4,5-*b*]indoles remains challenging.



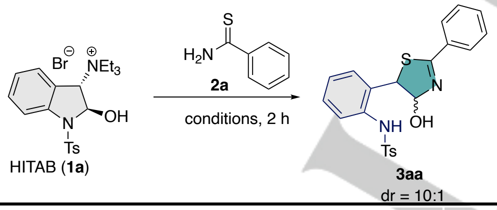
Scheme 1. (A) and (B) State-of-art construction of thiazolo[4,5-*b*]indoles; (C) Our previous work; (D) This work.

Recently, we described the synthesis of 2-arylindoles via a ring-switch reaction of the 3-amino-2-hydroxyindolines under the transient tautomeric control of the hemiaminals,[9] which could be derived from HITAB (**1**, 2-hydroxyindoline-3-triethylammonium bromide)[10] and anilines (Scheme 1C). In order to develop the ring-switch reaction of indoles via the C2-N1 bond breaking transformations,[11-14] we herein wish to disclose the unprecedented reactions of indoline hemiaminals affords 2,5-diaryl-4-hydroxythiazolines through a thioamidation/ring switch sequence under the transient tautomeric control (sp^3- and sp^2-type: Scheme 1D). Furthermore, our protocol would enable 2,5-diarylthiazolidines to serve formally as new thiazolo[4,5-*b*]indole sp^2-type: surrogates by dehydrative cyclization using $BF_3{\bullet}OEt_2$ to afford dihydrothiazolo[4,5-*b*]indoles (sp^3-type). The successful development would offer access to thiazolo[4,5-*b*]indoles (sp^2-type) through the oxidation.

Results and Discussion

First, the reaction conditions for the synthesis of 2,5-diarylthiazolidine were optimized using HITAB (**1a**) and phenylthioamide (**2a**) as the substrate (Table 1). Contrast with our previous work,[9] the reactions in the absence of Et_3N[15] gave good yields probably due to its instability of the compound **3aa** with 10 : 1 dr (runs 1–3). When DMF was replaced with AcOEt, almost the same yields were observed (runs 4–5). When the reaction was conducted under the dilute conditions, the best yield was obtained (run 6). The use of MeCN as the solvent delivered **3aa** in 86% yield (run 7). Thus, the optimal reaction conditions were decided [**1a** (1 equiv.), **2a** (1 equiv.), AcOEt (0.033 M), reflux]. This is the first example for the synthesis of 2,5-diarylthiazolidine through the C2-N1 bond cleavage of the indole ring.[16-17]

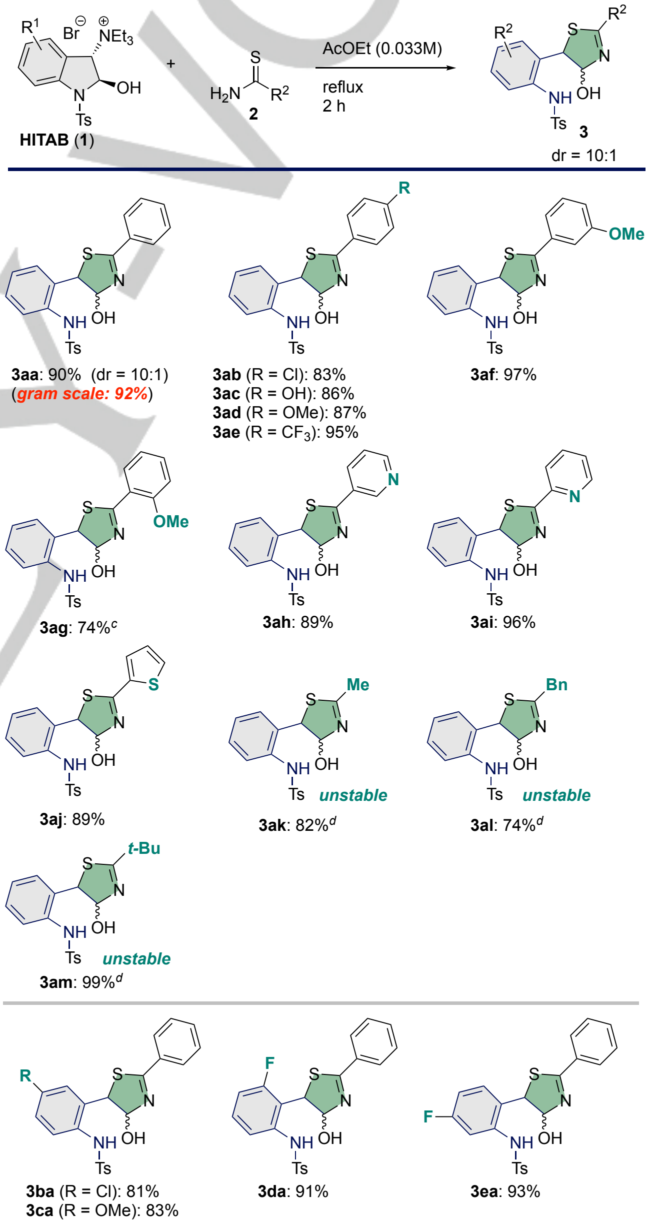
Table 1. Reaction condition optimization.



run[a]	equiv. of **2a**	Base	Solvent (M)	Temp., (°C)	yield (%)[b] of **3aa**
1	2	-	DMF (0.1 M)	100	80
2	1.1	-	DMF (0.1 M)	100	72
3	1.1	Et_3N	DMF (0.1 M)	100	Complex mixture
4	1.1	Et_3N	AcOEt (0.1 M)	reflux	67
5	1	-	AcOEt (0.1 M)	reflux	73
6	**1**	**-**	**AcOEt (0.033 M)**	**reflux**	**90**
7	1	-	MeCN (0.033 M)	reflux	86

[a] Reaction conditions: **1a** (0.5 mmol) and **2a** (0.5 x X mmol) in solvent (5 or 15 mL). [b] Isolated yields.

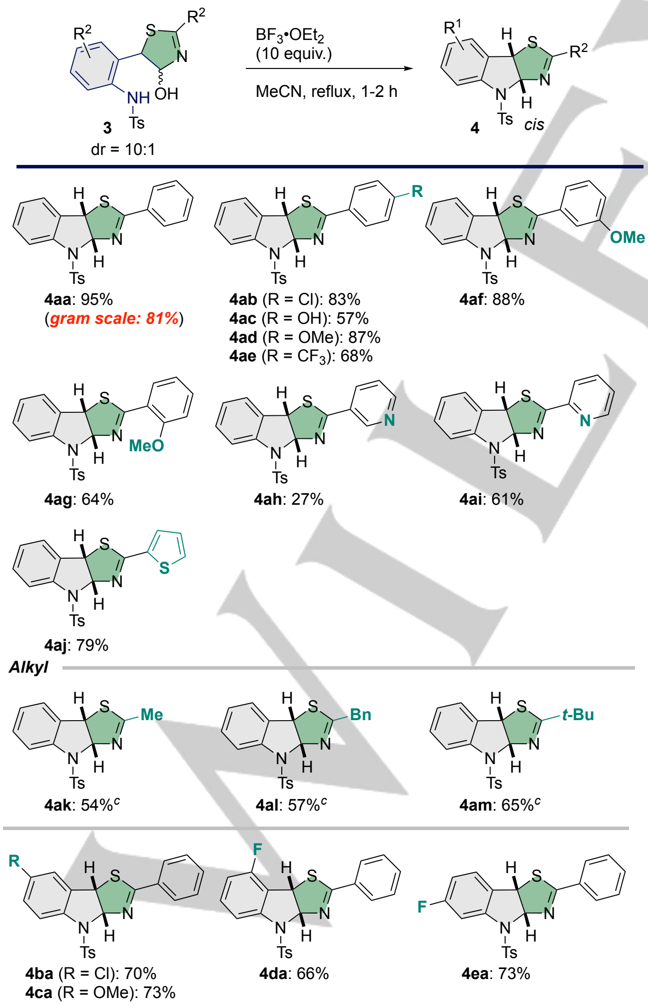
Next, the scope of this new ring-switch reaction of indoles was evaluated by varying the substrate (Scheme 2). The effect of the substituents on the yields of the **3** was examined. 4-Substituted phenylthioamides all proceeded smoothly to deliver the desired products **3ab**, **3ac**, **3ad**, and **3ae** in 63%, 45%, 87%, and 95%, respectively. The reactions of 2- or 3-substituted phenylthioamides afforded good yields (**3af** and **3ag**). It was found that pyridylthioamides all proceeded smoothly, delivering the desired products **3ah** and **3ai** in 89% and 96%, respectively. It is noteworthy that the reaction of thiophen-thioamide was found to participate in our transformation (**3aj**).



Scheme 2. Substrate scope[a,b]: [a] Reaction conditions: **1** (0.5 mmol) and **2** (0.5 mmol) in AcOEt (15 mL). [b] Isolated yields. [c] Reaction time: 8 h. [d] Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol) and Et_3N (2.5 mmol) in AcOEt (15 mL), reflux, 15 min.

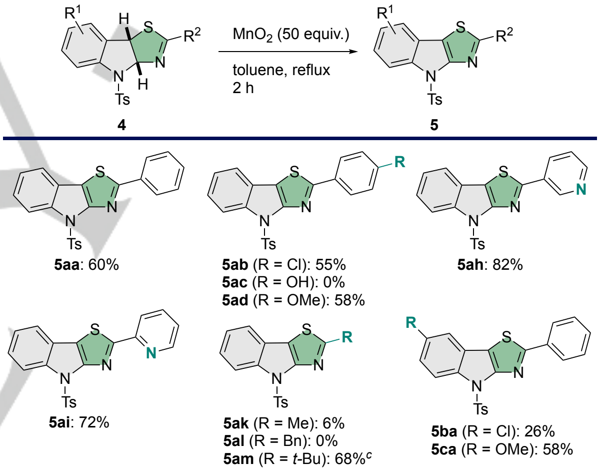
However, alkylthioamides are not compatible in the reaction maybe due to the instability of the products **3ak**, **3al** and **3am**. After intensive investigations, we found that the conditions using Et_3N for shorten reaction time were essential for the operation of the reaction of alkylthioamides. Thus, the reaction under the conditions using Et_3N in AcOEt for 15 min afforded the desired products **3ak**, **3al** and **3am** in 82%, 74%, and 99%, respectively. Either electron-withdrawing or electron-donating groups on the indole ring were suitable for our transformation (**3ba** and **3ca**). 4-Substited or 6-substituted HITABs were also tolerated under the reaction conditions (**3da** and **3ea**). To showcase the scalability, the reaction was conducted on a gram scale (5 mmol scale). To our delight, our transformation afforded **3aa** in 92% yield without any modification.

To show the synthetic potential of our protocol, we then examined the dehydrative cyclization of 2,5-diaryl-4-hydroxythiazolines (Scheme 3). The dehydrative cyclization of **3** (dr = 10:1) could be carried out by $BF_3•OEt_2$ to afford dihydrothiazolo[4,5-*b*]indole **4aa** in 95% yield. The reaction was also suitable for the gram-scale synthesis of **4aa** in 82% yield with slight loss of yield. Both substituted phenyl ring and pyridines were also applicable to this dehydrative cyclization, delivering **4ab**–**4aj** in 27–88% yields. Notably, unstable alkyl-substituted hydroxythiazolines were tolerated, affording the corresponding products **4ak**, **4al** and **4am** in 54%, 57%, and 65% yields, respectively. Anilines with different functional groups could afford the desired products (**4ba**, **4ca**, **4da**, and **4ea**).



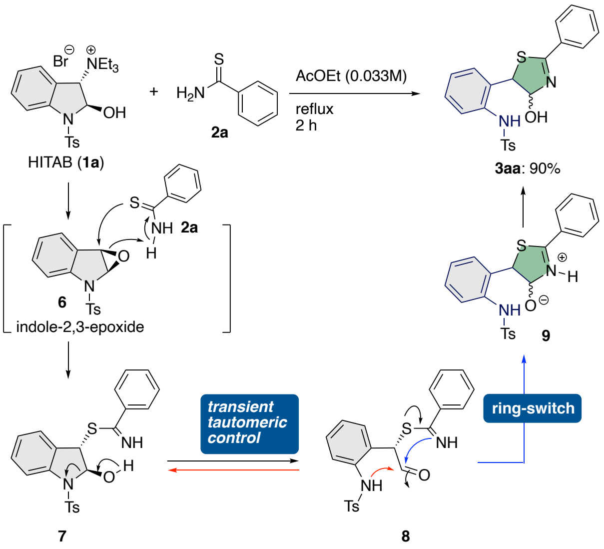
Scheme 3. Dehydrative cyclizations [a,b]: [a] Reaction conditions: **3** (0.2 mmol) and $BF_3•OEt_2$ (2 mmol) in MeCN (6 mL). [b] Isolated yields. [c] Reaction time: 24 h.

Considering that dihydrothiazolo[4,5-*b*]indoles might be valuable precursor for access to thiazolo[4,5-*b*]indoles, oxidative transformations were performed (Scheme 4). Some oxidants resulted in unsuccess due to the instability of the aminal moieties. Subsequently, a series of thiazolo[4,5-*b*]indoles **5aa**–**5ca** were synthesized by MnO_2-conditions. To our delight, thiazolo[4,5-*b*]indoles bearing pyridyl moieties all yielded products **5ah**, **5ai** in good yields. The unstable alkyl-substituted hydroxythiazolines were also tolerated, affording the corresponding products **5ak**, and **5am** in 6% and 68% yield, respectively. However, the conditions were unsuitable for some substrates such as the compound **4ac** containing 4-hydroxyphenyl group and the compound **4al** containing benzyl group, presumably due to the high reactivity against the oxidant.



Scheme 4. Synthesis of thiazolo[4,5-*b*]indoles by oxidations[a,b]: [a] Reaction conditions: **4** (0.1 mmol) and MnO_2 (5 mmol) in toluene (8 mL). [b] Isolated yields. [c] Reaction time: 15 min.

On the basis of the above results and previous reports, we proposed a possible reaction mechanism (Scheme 5). First, the indole-2,3-epoxide **6**[10,15] generated in situ undergoes nucleophilic attack by phenylthioamide **2a** to afford benzimidothioate **7**. Transient tautomeric control[9] would afford α-thioaldehyde **8**, and subsequent cyclization by the imidate moiety/protonation furnish 2,5-diaryl-4-hydroxythiazoline **3aa**. [18] These sequences delineates the first example of construction of thiazoline from the indoles through the ring-switch reaction.[11-14,16-17]



Scheme 5. Possible reaction mechanism.

Conclusions

Here we show that the unexpected reactions of indoline hemiaminals affords 2,5-diaryl-4-hydroxythiazolines through a thioamidation/ring switch sequence. Further transformations of the thiazolines provide a direct entry to dihydrothiazolo[4,5-*b*]indoles and thiazolo[4,5-*b*]indoles. The current methodology provides a new synthetic method for the synthesis of diverse thiazoline derivatives through "open and shut" transformation. [19]

Experimental Section

General experimental details, characterization, as well as copies of ^{1}H and ^{13}C NMR spectra can be found in the online Supporting Information.

General procedures for the thioamidation/ring-switch of 1 with thioamides 2a-j (Scheme 2): To a solution of HITAB **1** (0.5 mmol) in AcOEt (15 mL, 0.033 M) was added thioamide **2** (0.5 mmol) at room temperature. The mixture was stirred under reflux conditions for 2 hours. After addition of H_2O at room temperature, the whole was extracted with AcOEt (3 x 25 mL), washed with brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/20 to 1/2) to give **3**.

General procedures for the dehydrative cyclization of 3 with BF_3•OEt_2 (Scheme 3): To a solution of hydroxythiazoline **3** (0.2 mmol) in MeCN (6 mL, 0.033 M) was added BF_3•OEt_2 (2.0 mmol) at room temperature. The mixture was stirred under reflux conditions until the complete disappearance of starting material as indicated by TLC. After addition of H_2O and saturated aqueous sodium hydrogen carbonate at room temperature, the whole was extracted with $CHCl_3$ (3 x 25 mL), washed with brine (25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/5 to1/2) to give **4**.

General procedures for the oxidation of dihydrothiazolo[4,5-*b*]indoles with MnO_2 (IV): (Scheme 3): To a solution of hydroxythiazoline **4** (0.1 mmol) in toluene (8 mL, 0.0125 M) was added MnO_2 (5 mmol) at room temperature. The mixture was stirred under reflux conditions until the complete disappearance of starting material as indicated by TLC. After cooling down, the whole was filtrate with Celite, washed with AcOEt (10 mL), MeOH (10 mL) and $CHCl_3$ (10 mL). The organic layer was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/3) to give **5**.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: indoles • ring-switch • thiazolo[4.5-*b*]indoles• hemiaminals • thioamides

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Heterocycles

Consice Synthesis of Thiazolo[4.5-*b*]indoles via Ring Switch/Cyclization Sequences

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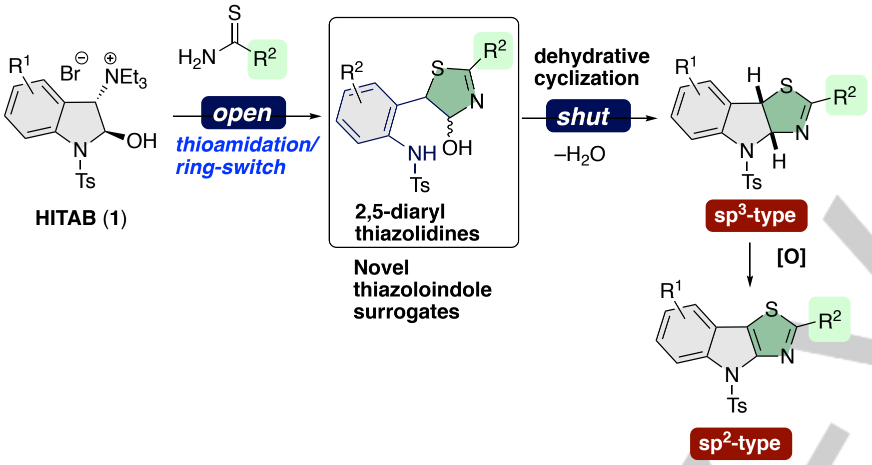

Open and shut!!: Unprecedented modular synthesis of thiazolo[4.5-*b*]indoles was accomplished by a unique ring switch/cyclization sequences of hemiaminals.