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A Stepwise Synthesis of Spiroindoline Compounds via Ring Opening of Aziridines and C-H Activation/Cyclization

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Abstract. A type of 2,2-disubstituted N-sulfonylaziridines bearing OTBS groups and aryl groups at two different substitutions of the aziridine ring has been prepared. Based on them, a stepwise strategy involving ring opening of aziridines and C-H activation/cyclization has been developed for the general synthesis of spiroindoline pyrans and spiroindoline furans.

Keywords: Spiroindoline compounds; Aziridines; Ring opening; C-H activation; Synthetic strategy

Introduction

Spiroindoline scaffolds represent privileged structures encountered in a lot of natural products, as well as synthetic compounds with interesting biological properties[1]. Moreover, such skeletons are also a good complement to numerous flat cyclic compounds as potential candidates for drug discovery due to their unique three-dimensional shape. It is not surprising that the construction of spiroindoline scaffolds has attracted much attention from chemists[2]. In particular, spiroindoline furans[3] and spiroindoline pyrans[4], as two important categories of spiroindolines, are also frequently found in many natural products, pharmaceuticals, and biologically active compounds (Figure 1). Typical strategies for the synthesis of these valuable spirocyclic compounds include formal [3+2] and [3+3] cycloadditions of isatins[5], formal [4+1] cycloadditions of 3-diazoindolin-2-ones[6], cyclizations of isatin diketals[7], cyclizations of 3-hydroxyoxindoles[8], intramolecular enyne metathesis of oxindole enynes[9] and dearomatization reactions of 3-substituted indoles[10], etc. Noticeably, these methods generally rely on manipulation indole derivatives, which need to be pre-prepared by multistep synthesis. Therefore, the development of a straightfoward and flexible strategy[11] allowing more diversified syntheses of spiroindoline furans and spiroindoline pyrans from simple starting materials is still highly desirable.

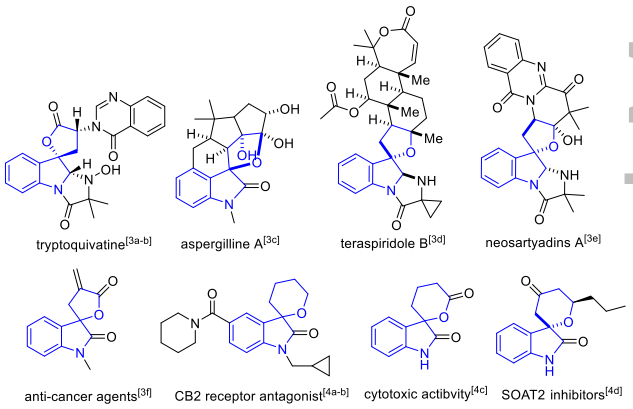
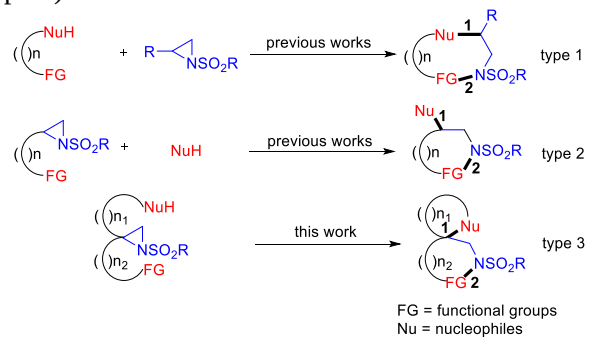


Figure 1. Representative bioactive molecules.

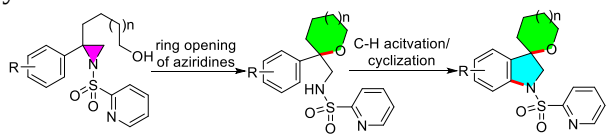
N-Sulfonylaziridines[12], which are easily accessible and stable, react readily with various nucleophiles to provide ring-opening products. Combining ring opening of N-sulfonylaziridines with other reactions such as nucleophilic substitution of alkyl halides[13], Michael addition[14], addition of alkyne[15], Buchwald-Hartwig reaction[16], Pictet–Spengler reaction[17] and C-H activation[18], synthetic chemists have developed a lot of elegant cascades to access various cyclic compounds (Scheme 1, type 1 and type 2). However, there are few reports on the assembly of spirocyclic compounds by cascades involving ring opening of N-sulfonylaziridines in the known literature[19]. In this context, we envisage the synthesis of a new type of 2, 2-disubstituted N-

sulfonylaziridines[19, 20]. Nucleophiles and functional groups such as alkyl halides, electron-deficient alkenes, alkynes, aryl halides or arenes are simultaneously introduced to the two different substitutions of the aziridine ring. These aziridines undergo ring opening of N-sulfonylaziridines and ring closing between the newly generated nitrogen anions and those functional groups to provide the spirocyclic compounds as the products (Scheme 1, type 3).



Scheme 1. Cascades involving ring opening of N-sulfonylaziridines.

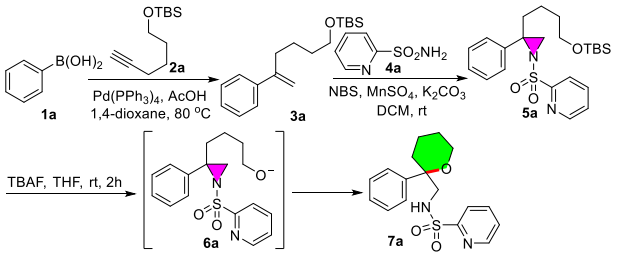
With these considerations in mind, we selected alcohols as the nucleophiles and arenes as the functional groups required by ring closing to begin our study on the strategy for the construction of spirocyclic compounds. Fortunately, ring opening of N-sulfonylaziridines followed C-H activation/cyclization[21] took place smoothly to furnish a series of spiroindoline compounds in good yields (Scheme 2). The advantages of this strategy included good atomic economy, high bonding efficiency and cyclization efficiency, broad scope of substrates and good generality of the ring size in product. It provided a good choice for the general and efficient construction of spiroindoline skeletons, which was particularly well suited for the preparation of spiroindoline compound libraries. Herein, we would like to report our detailed results on the cyclization reaction.



Scheme 2. Construction of spiroindoline skeletons.

Results and Discussion

Our study began with the preparation of the required aziridine **6a** in a three-step sequence (Scheme 3). Coupling reaction[22] of phenylboronic acid **1a** with alkyne **2a** generated alkene **3a** in 70% yield. Then aziridination[20a] of alkene **3a** with sulfonamide **4a** provided aziridine **5a** in 35% yield. At last, removal of tert-butyldimethylsilyl group was carried out by the treatment of aziridine **5a** with TBAF in THF. Interestingly, the oxygen anion **6a**, generated by desilylation, further took place intramolecular ring opening of the aziridine to provide product **7a** in 95% yield.



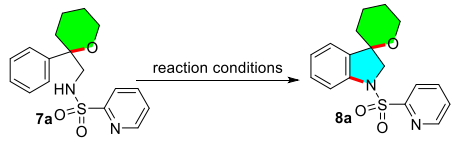
Scheme 3. The preparation of the starting material.

With the unexpected ring-opening product **7a** in hand, further C-H activation/cyclization was investigated for the synthesis of spiroindoline pyran **8a** (Table 1). Initially, treatment of **7a** in the presence of 5 mol % of $Cu(OAc)_2$ and 4Å MS (160 mg) in DMF in the opening air at 140 °C for 36 h led to the desired product **8a** in 20% yield (entry 1). When we increased the amount of $Cu(OAc)_2$ from 5 mol % to 200 mol %, the yield of **8a** was remarkably improved from 20% to 63% (entry 2). Then K_2CO_3 and Et_3N were added into the reaction system to improve the yield of product **8a**, respectively (entries 3-4). Unfortunately, no better results were obtained. Next, the influence of the temperature for the formation of **8a** was tested (entries 5 and 6). When the reaction was performed at 120 °C, product **8a** was only furnished in 19% yield. By contrast, raising the temperature to 160 °C was found to be in favour of the formation of product **8a**, which was provided in 72% yield. After that, DMA was selected as the reaction solvent instead of DMF (entry 7). No improved yield was observed and product **8a** was afforded in 50% yield. At last, 10 mol % of $Pd(OAc)_2$ was attempted to be added to the reaction as well (entry 8). It was found that the yield of product **8a** was decreased from 72% to 68%.

To generalize our approach, several aziridines **5b–5m** having different substituents at the benzene ring and the pyridine ring were subjected to the stepwise cyclization for the construction of spiroindoline pyrans (Table 2). First, it was found that aziridines with various R^1 substituents residing at different positions on the benzene ring led to products **8** in acceptable to good yields. When cyclization of aziridines **5b-5h** bearing R^1 substitutions at the *para*-position on the benzene ring were preformed, a lot of groups like F, Cl, CN, CO_2Me, CF_3, Me and Ph group were well tolerated to provide products **8b-8h** in 45%-85% yields (entries 2-8). Among them, the relative configuration of **8g** was unambiguously confirmed by X-ray crystal structure analysis[23]. For aziridines **5i** and **5j** with R^1 substitutions at the *meta*-position on the benzene ring, a 1:1 mixture of two regioselective products were provided in good yields (entries 9-10). With regard to aziridine **5k** with a F

group at the *ortho*-position on the benzene ring, the stepwise cyclization led to product **8k** in 54% yield (entry 11). Besides, aziridine **5l** with two methyl groups at the *meta*-position on the benzene ring was also subjected into the stepwise cyclization (entry 12). The corresponding product **8l** was furnished in 60% yield. Then we turned our attention to investigate the influence of R^2 substitution on the pyridine ring for the stepwise cyclization. It was found that the methyl group on the pyridine ring was beneficial for the stepwise cyclization, providing product **8m** in 72% yield (entry 13).

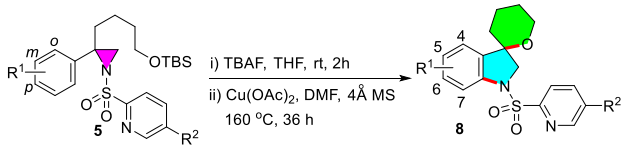
Table 1. Optimization of the Reaction Conditions for C-H activation[a)]



Entry	Reaction conditions	Yield/%[b)]
1	5 mol % $Cu(OAc)_2$, DMF, 140 °C	20
2	200 mol % $Cu(OAc)_2$, DMF, 140 °C	63
3	200 mol % $Cu(OAc)_2$, 200 mol % K_2CO_3, DMF, 140 °C	-
4	200 mol % $Cu(OAc)_2$, 200 mol % Et_3N, DMF, 140 °C	43
5	200 mol % $Cu(OAc)_2$, DMF, 120 °C	19
6	200 mol % $Cu(OAc)_2$, DMF, 160 °C	72
7	200 mol % $Cu(OAc)_2$, DMA, 160 °C	50
8	200 mol % $Cu(OAc)_2$, 10 mol % $Pd(OAc)_2$, DMF, 160 °C	68

[a)] All reactions were carried out with **7a** (1 equiv., 0.2 mmol) in solvent (6 mL) in the presence of 4Å MS (160 mg) in the open air for 36 h; [b)] Isolated yields.

Table 2. Construction of spiroindoline pyran skeletons[a)]

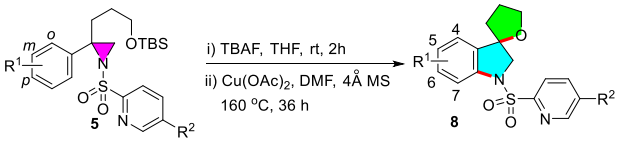


Entry	**5** R^1/R^2	**8** R^1/R^2	Yield/%[b)]
1	**5a** H/H	**8a** H/H	68
2	**5b** *p*-F/H	**8b** 6-F/H	45
3	**5c** *p*-Cl/H	**8c** 6-Cl/H	57
4	**5d** *p*-CN/H	**8d** 6-CN/H	72
5	**5e** *p*-CO_2Me/H	**8e** 6-CO_2Me/H	63
6	**5f** *p*-CF_3/H	**8f** 6-CF_3/H	61
7	**5g** *p*-Me/H	**8g** 6-Me/H (X-Ray)	64
8	**5h** *p*-Ph/H	**8h** 6-Ph/H	85
9	**5i** *m*-Cl/H	**8i** 5-Cl/H **8i'** 7-Cl/H	34 34
10[c)]	**5j** *m*-OMe/H	**8j** 5-OMe/H **8j'** 7-OMe/H	70
11	**5k** *o*-F/H	**8k** 8-F/H	54
12	**5l**	**8l**	60
13	**5m** H/Me	**8m** H/Me	72

[a)] All reactions were performed on 1 mmol scale; [b)] Isolated yields; [c)] **8j** : **8j'** = 1:1.

After the successful synthesis of spirodoline pyrans, this stepwise strategy involving ring opening of aziridines and C-H activation/cyclization could be also successfully expanded to the construction of spiroindoline furans (Table 3). When aziridine **5n** was used as the substrate, the desired product **8n** was afforded in 50% yield (entry 1). For aziridines bearing R^1 substitutions at the *para*-position of the benzene ring, it was found that Cl and Ph groups were tolerated to furnish products **8o-8p** in 43-48% yields (entries 2-3). Besides, cyclization of aziridine **5q** with R^2 substitution on the pyridine ring possessing a Me group took place smoothly to afford product **8q** in 63% yield (entry 4).

Table 3. Construction of spiroindoline furans[a)]

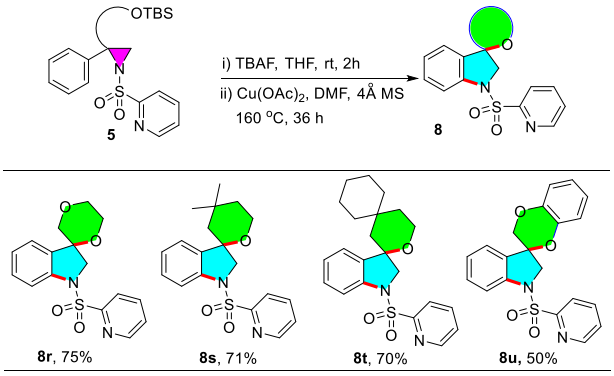


Entry	**5** R^1/R^2	**8** R^1/R^2	Yield/%[b)]
1	**5n** H/H	**8n** H/H	50
2	**5o** *p*-Cl/H	**8o** 6-Cl/H	48
3	**5p** *p*-Ph/H	**8p** 6-Ph/H	43
4	**5q** H/Me	**8q** H/Me	63

[a)] All reactions were performed on 1 mmol scale; [b)] Isolated yields.

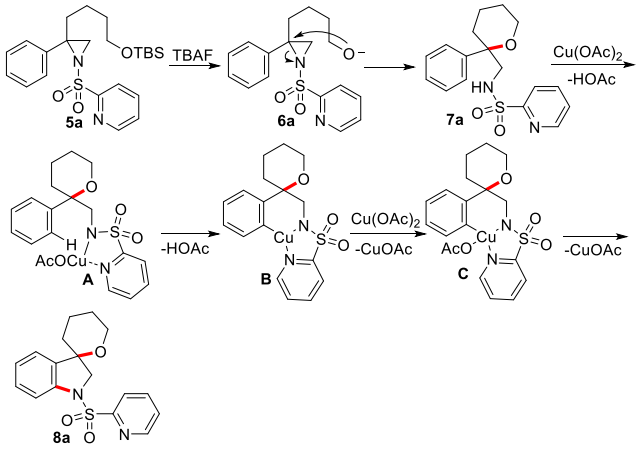
In order to further broaden the application scope of the stepwise cyclization, aziridines **5r-5u** having different tethers between the aziridine and the OTBS group were synthesized (Table 4). First, the oxygen atom was introduced into the tether between the aziridine and the OTBS group. It can be seen that the corresponding product **8r** was afforded in 75% yield (entry 1). Then aziridine **5s** bearing two methyl groups in the tether was synthesized. Under the optimized conditions, the reaction proceeded smoothly to afford the desired product **8s** in 71% yield (entry 2). Next, changing two methyl groups to the cyclic group in the tether had no significant influence on the reaction, providing product **8t** in 70% yield (entry 3). Finally, it was found aziridine **5u** containing the benzene ring and the oxygen atom in the tether was suitable substrate for the stepwise cyclization. The desired product **8u** was furnished in 50% yield.

Table 4. Construction of spiroindoline skeletons[a-b)]



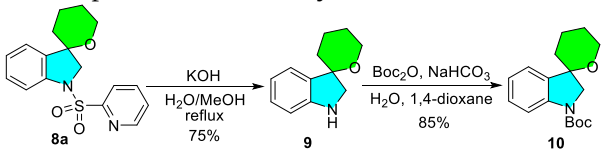
[a] All reactions were performed on 1 mmol scale; [b] Isolated yields.

A possible mechanism was proposed for the present stepwise cyclization (Scheme 4). Treatment of aziridine **5a** with TBAF provided the oxygen anion **6a**, which further underwent intramolecular ring opening of aziridines to afford **7a**. Then coordination between **7a** and $Cu(OAc)_2$ took place to generate intermediate **A** and AcOH. Next, intermediate **A** underwent intramolecular C-H activation to afford intermediate **B** along with the generation of another AcOH. After that, intermediate **B** was converted into intermediate **C** by $Cu(OAc)_2$-promoted oxidation. At last, intermediate **C** underwent reductive elimination to provide product **8a** along with the release of CuOAc.



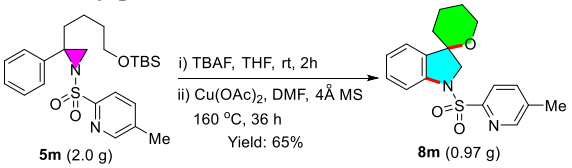
Scheme 4. A possible mechanism for the stepwise cyclization.

Several transformations of product **8a** were carried out (Scheme 5). The pyridine-2-sulfonyl group of **8a** could be removed by KOH in a mixture solvent of H_2O and MeOH under reflux, providing product **9** in 75% yield. Further treatment of **9** with Boc_2O furnished product **10** in 85% yield.



Scheme 5. Further Transformation of spiroindoline **8a**.

Finally, the stepwise spirocyclization of aziridine **5m** was conducted on gram scale under the optimized reaction conditions (Scheme 6). It can be seen that a slightly decreased yield of product **8m** was successfully provided.



Scheme 6. Stepwise spirocyclization of **5m** in gram scale

Conclusion

In conclusion, a stepwise cyclization of 2,2-disubstituted N-sulfonylaziridines with aryl groups and OTBS groups at the two different of substitutions of the aziridine ring have been described. A series of spiroindoline pyrans and spiroindoline furans were afforded in moderate to good yields via ring opening of aziridines and C-H activation/cyclization. This strategy involved the formation of two new rings, one new C-O bond and one new C-N bond, allowing the general and efficient construction of libraries of spiroindoline compounds. Further investigations on the cyclization of this kind of substrates for the synthesis of other valuable spirocyclic compounds will be reported in due course.

Experimental Section

Step i: To a stirred solution of aziridine **5** (1 mmol, 1.0 equiv.) in anhydrous THF (5 mL) was added TBAF (2 mmol, 2.0 equiv., 1 M in THF) dropwise under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (5 mL) and water (5 mL). The phases were separated, the organic layer was washed with brine (2 x 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and filtered through a short column (silica gel, 3 x 4 cm) eluting with (petroleum ether/ethyl acetate, 3:1~2:1). After evaporation of the solvent, the residue was subjected into step ii.

Step ii: The above residue was dissolved in DMF (30 mL/mmol) and then $Cu(OAc)_2$ (2.0 equiv), 4 Å MS (800 mg/mmol) was added, the mixture was stirred vigorously at 160 °C in the open air for 36 h. After cooled to room temperature, the solvent DMF was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 3:1) to afford product **8**.

Acknowledgements

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[23] CCDC-2026450 (**8g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. ORTEP drawing of **8g** can be found in supporting information.

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FULL PAPER

A Stepwise Synthesis of Spiroindoline Compounds via Ring Opening of Aziridines and C-H Activation/Cyclization

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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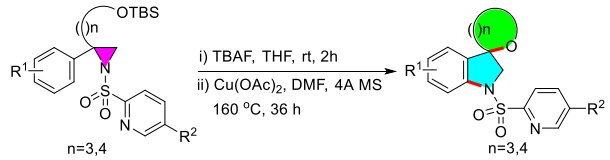

- R^1=H, F, Cl, CN, CF_3, CO_2Me, Me, Ph and OMe, R^2=H, Me
- formation of one C-O bond and one C-N bond, two new rings
- rapid and efficient construction of spiroindoline furans and pyrans