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# COMMUNICATION

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## Unified strategy to access 6*H*-benzofuro[2,3-*b*]indoles and 5,6dihydroindolo[2,3-*b*]indoles via UV light-mediated diradical cyclization

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**Abstract:** A unified protocol for the construction of 6*H*-benzofuro[2,3-*b*]indoles and 5,6-dihydroindolo[2,3-*b*]indoles via UV light-mediated diradical cyclization was developed and preliminary efforts were also made to functionalize at C10b position of 6*H*-benzofuro[2,3-*b*]indoles. This mild and facile strategy may have great potential in the syntheses of natural products and functional materials.

**Keywords:** UV light-mediated; diradical cyclization; *6H*-benzofuro[2,3-*b*]indole; 5,6-dihydroindolo[2,3-*b*]indole.

Indole derivatives are one of the most important nitrogen-containing heterocycles with wide-spectrum bioactivities and diverse structures.<sup>[1]</sup> Among them, 6*H*-benzofuro[2,3-*b*]indoles 5.6and dihydroindolo[2,3-b]indoles, two intriguing classes of heterocycle-fused indoles, have attracted tremendous attention owing to their wide applications in OLED).<sup>[2]</sup> functional materials (such as pharmaceutical/medicinal chemistry<sup>[3]</sup> and other scientific fields. Especially, C10b functionalized 5a,10b-dihydro-6*H*-benzofuro[2,3-*b*]indoles widely distributed in quite a number of natural products such as diazonamide A and azonazine (Figure 1), had raised broad interest from organic community, and a variety of efficient approaches to build this framework were developed, including intramolecular [3+2] annulation, intramolecular electrosynthesis, and iminium-catalyzed cascade process, among others.<sup>[4]</sup>

In contrast, only a few methods for the construction of 6*H*-benzofuro[2,3-*b*]indoles and 5,6dihydroindolo[2,3-b]indoles have been reported. The major synthetic approaches to 5,6-dihydroindolo[2,3] b]indoles include two classes: (i) Pd-mediated C-I/C-H or oxidative C-H/C-H coupling reaction (Scheme I. path (a)),<sup>[3,5]</sup> (ii) electrophilic amination of arene C-H bond,<sup>[6]</sup> Cadogan cyclization,<sup>[7]</sup> and iodine-mediated cyclization (path b).<sup>[8]</sup> As for 6H-benzofuro[2,3b]indoles, there are only two synthetic routes via copper-mediated coupling reaction<sup>[9]</sup> or oxidative cycloamination reaction<sup>[10]</sup> in literature. Given these often approaches require high temperatures. prefunctionalized substrates. multi-step and/or manipulation, developing a simple and practical method to access these heterocycle-fused indoles is still highly desirable.



**Figure 1.** Representative natural products diazonamide A and azonazine with C10b functionalized 5a,10b-dihydro-6*H*-benzofuro[2,3-*b*]indole structural unit.

During our ongoing work for facile construction of spiro[indazole-3,3'-indolin]-2'-ones via 1,3-dipolar

cycloaddition of arynes with 3-diazoindolin-2-ones, we found that indazolo[2,3-c]quinazolin-6(5H)-ones could be readily afforded from spiro[indazole-3,3'-indolin]-2'-ones through thermal isomerization.<sup>[11]</sup> As part of our continuous endeavour to develop other transformations of these unique azo spirooxindoles, we present herein a unified approach to synthesize 6H-benzofuro[2,3-b]indoles and 5,6-dihydroindolo[2,3-b]indoles via UV light-mediated diradical cyclization from this class of azo spirooxindoles and their N-analogues.



**Scheme 1.** Synthetic routes to 6*H*-benzofuro[2,3-*b*]indoles and 5,6-dihydroindolo[2,3-*b*]indoles

In modern organic synthesis, chemical transformations mediated by light are thought to be superior to conventional transition metal-catalyzed reactions, because light is a traceless, nonpolluting reagent,<sup>[12]</sup> and most of the current efforts are focused on visible light photoredox catalysis.<sup>[13]</sup> Reactions mediated by UV light are usually associated with multiple side pathways and poor functional group tolerance due to the high energy of UV light, but they usually do not require additional photocatalysts to sensitize organic molecules. Moreover, UV lightinduced extrusion of nitrogen from benzotriazole or indazole derivatives followed by diradical cyclization was early developed to prepare diverse heterocycles.<sup>[14]</sup> Recently, Movassaghi reported a series of total synthesis of dimeric alkaloids via diazene-directed fragment assembly strategy, further highlighting the importance and practicality of

diazene-based bond-forming chemistry.<sup>[15]</sup> Inspired by these advances, we wondered whether azo spirooxindoles could be transform into other useful scaffolds via UV light radiation. Thus, we allowed the spirooxindole 1a to be radiated with UV lamps. To avoid dimerization, we conducted the reaction in a highly diluted solution. To our delight, the desired diradical cyclization product 2a was obtained in 49% yield in THF with a concentration of 12 mM along with some unidentified side-products (Table 1, entry 1). Subsequent X-ray studies revealed that one of the side pathways was dimerization.<sup>[16]</sup> Further diluting the solution resulted in a higher yield (63%, entry 3), while lower concentration could not raise the yield of 2a (entries 4 and 5). When the solvent was changed from THF to DCM, PhMe, and CH<sub>3</sub>CN (entries 6-8), it was found that DCM and PhMe afforded comparable yields. However, CH<sub>3</sub>CN was found to be inferior probably because the C-N triple bond of CH<sub>3</sub>CN interfered with the radical reaction. Exposure of the reaction system to the air lowered the yield slightly (entry 9). When a different light source such as LED UV lamp (15 W) was employed, the reaction also proceeded smoothly but required longer time (entry 10).

Table 1. Optimization of reaction conditions<sup>[a]</sup>



| Entry             | Concentration<br>(mM) | Solvent            | Yield [%] <sup>[b]</sup> |
|-------------------|-----------------------|--------------------|--------------------------|
| 1                 | 12                    | THF                | 49                       |
| 2                 | 9                     | THF                | 59                       |
| 3                 | 6                     | THF                | 63                       |
| 4                 | 3                     | THF                | 63                       |
| 5                 | 0.8                   | THF                | 63                       |
| 6                 | 6                     | DCM                | 52                       |
| 7                 | 6                     | Toluene            | 60                       |
| 8                 | 6                     | CH <sub>3</sub> CN | 44                       |
| 9 <sup>[c]</sup>  | 6                     | THF                | 50                       |
| 10 <sup>[d]</sup> | 6                     | THF                | 55                       |

<sup>[a]</sup> *Reaction conditions:* **1a** (0.2 mmol), 250 W highpressure Hg UV lamp (365 nm), solvent, under N<sub>2</sub>.

<sup>[b]</sup> Isolated yields of **2a**.

<sup>[c]</sup> Under air.

<sup>[d]</sup> 15 W LED UV lamp (365 nm) was used instead.

With the optimal reaction conditions in hand (Table 1, entry 3), we set out to explore the substrate scope of spirooxindoles prepared via 1,3-dipolar cycloaddition of arynes with 3-diazoindolin-2-ones. As shown in Table 2, substrates bearing various N-R<sup>3</sup>

including allyl and propargyl groups were all applicable to this radical reaction. affording corresponding 6*H*-benzofuro[2,3-b] indoles (2a-f) in 41–63% yields. Next, substrates with various  $R^1$  on the benzene moiety of the oxindole were studied and it was found that all of them except for 1n with 9-OMe provided the desired products in moderate yields (2g-n). Notably, it is interesting that bromo group could survive under this radical conditions (2j-l), which is useful handle for derivatizing to get OLED materials.<sup>[2]</sup> The substituent of R<sup>2</sup> on the benzene moiety of indazole was also examined, and it revealed that either electron-donating group (e.g., **10-q**) or electron-withdrawing group (e.g., **1r**) had no pronounced effect on the yields of the radical reaction.

 Table
 2.
 Scope of diradical reaction of spiro[indazole-3,3'-indolin]-2'-ones<sup>[a]</sup>



<sup>[a]</sup> Reaction conditions: 1 (0.2 mmol), 250 W high-pressure Hg UV lamp (365 nm), THF (33 mL), under  $N_2$ , 4–10 h. Isolated yield.

With the successful construction of 6Hbenzofuro[2,3-*b*]indoles via UV light-mediated diradical reaction, we wondered whether 5.6dihydroindolo[2,3-b]indoles could be accessed in a similar fashion. Following the same procedure, we prepared a library of spiro[indazole-3,3'-indolin]-2'imines (1s-x) from 3-diazoindolin-2-imines and benzynes.<sup>[17]</sup> Note that although 3-diazoindolin-2imines had been successfully applied in a range of reactions to prepare diverse heterocycles via transition metal-catalyzed carbene reactions,<sup>[18]</sup> there have been no reports to date on their use as 1,3dipoles. Then spiro[indazole-3,3'-indolin]-2'-imines 1s-x were subjected to UV radiation and all of them proceeded smoothly to afford 5,6-dihydroindolo[2,3*b*]indole derivatives (2s-x) in moderate yields (Table 3). As shown in Table 3, it was clear that substrates with *N*-Ms performed better than those with *N*-Ts for this diradical reaction (2s versus 2v, 2u versus 2x).

 Table 3.
 Scope of diradical reaction of spiro[indazole-3,3'-indolin]-2'-imines<sup>[a]</sup>



<sup>[a]</sup> *Reaction conditions:* **1** (0.2 mmol), 250 W highpressure Hg UV lamp (365 nm), THF (33 mL), under N<sub>2</sub>, 4–10 h. Isolated yield.

Fascinated by natural products diazonamide A and azonazine containing a C10b functionalized 5a,10bdihydro-6H-benzofuro[2,3-b]indole core, we set out to explore the derivation reaction at the C10b position of 6*H*-benzofuro[2,3-*b*]indole (Scheme 2). Interestingly, when 2a was treated with TsOH·H<sub>2</sub>O, 3a was obtained in 98% yield via an acid-mediated ring-opening reaction. While using anhydrous TsOL and allyl alcohol, 4a was obtained via an acidpromoted ring-opening and Claisen-rearrangemen. cascade process along with a small amount of 3a. 3a and 4a could be transformed into 6a through a multistep manipulation according to the literature.<sup>[19]</sup> At this stage, we have developed a novel route to C10b functionalized 5a,10b-dihydro-6H-benzofuro[2,3blindoles through ring-opening and recyclization strategy. However, bromination at C10b using NBS/NaBH<sub>4</sub> failed to deliver the desired bromination product 5a, and an unidentified product was isolated.



Scheme 2. Diverse transformations.

In accordance with the previous reports,<sup>[14]</sup> the plausible diradical mechanism for the formation of 2a was proposed and shown in Scheme 3. Initially,

spiro[indazole-3,3'-indolin]-2'-one **1a** undergoes decomposition to release N<sub>2</sub> under the radiation of UV light and then forms diradical intermediate **7a**.<sup>[20]</sup> Next intramolecular diradical cyclization forms a new C-O bond and delivers the desired **2a**. On the other hand, intermediate **7a** could also undergo H-abstraction and then dimerize to afford a dimer **9a**,<sup>[21]</sup> which has been demonstrated by X-ray studies.<sup>[16]</sup>



Scheme 3. Proposed mechanisms.

In summary, a facile UV light-mediated diradical cyclization was developed to construct 6*H*-benzofuro[2,3-*b*]indoles and 5,6-dihydroindolo[2,3-*b*]indoles from azo spirooxindoles and their *N*-analogues. The success of this method highlights the importance and practicality of UV light-mediated reactions, as it provides the core structures for further derivatization either for natural product synthesis or for material synthesis.

#### **Experimental Section**

A solution of 1'-benzylspiro[indazole-3,3'-indolin]-2'-one **1** (0.20 mmol) in THF (33 mL) in schlenk quartz tube was degassed, refilled with  $N_2$  for three times, and then radiated with 250 W high-pressure Hg UV lamp (365 nm) for 4–10 h. The tube was surrounded with cold water to keep the temperature of the solution in tube at 20-25 °C. When **1** was almost completely depleted by monitoring on TLC, the solvent was removed and the resulting residue was purified by flash column chromatography to give **2**.

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

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