Highly Efficient and Stereoselective Construction of Bispirooxindole Derivatives via a Three-Component 1,3-Dipolar Cycloaddition Reaction

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A highly regio- and stereoselective synthesis of bispirooxindoles by 1,3-dipolar cycloaddition of in situ generated azomethine ylides from isatin and proline to different electron-deficient olefins has been developed. The synthesis affords the desired bispiro scaffold compounds in excellent yields with high regioselectivity under mild conditions. The stereochemistry was determined by single-crystal X-ray analysis.

Figure 1. Examples of biologically active spirooxindole derivatives.

Introduction

The development of highly efficient methods to construct spiro compounds have been a hot topic of great relevance in organic synthesis due to the pronounced biological activities of this class of compounds.[1] In particular, the spirooxindole ring systems, which widely exist in a variety of natural and unnatural products, are attractive synthetic targets.[2, 3] Recently, significant research efforts have been focused on the strategy for construction of spiro 3,3'-cyclooxindoles in medicinal and agricultural chemistry due to their unique biological activity, such as spiro 3,3'-cyclooxindoles A, B, C and D (Figure 1).[4] A variety of synthetic methods have been developed to access analogous compounds possessing the spirocyclic oxindole skeleton at the C3 position of the oxindole core.[4] Moreover, the fusion of oxindole motifs with different heterocycles or heteroatoms for the formation of diverse spirocyclic oxindoles have also attracted significant attention.[5]

Among the strategies for the construction of the framework of spirooxindoles,[6] it was noticed that 1,3-dipolar cycloaddition of azomethine ylides, generated from the decarboxylative condensation of isatins with different amino acid, to various olefins represented an efficient method for the construction of spiro-fused oxindoles involving the pyrrolidine moiety (Scheme 1).[7, 8] Great efforts have been made towards the [3+2] cycloaddition of azomethine ylides generated from isatin with different olefins.[9, 10] This methodology is fascinating because it provides an efficient method to construct five-membered heterocycles. Furthermore, when the electron-deficient alkene is a trisubstituted cyclic compound, the bispiro product would be obtained. A few excellent examples have been reported for the construction of bispirooxindoles.[11] It is worth noting that Xie and Wang’s group have reported the construction of spiropyrrolidine bisoxindoles via 1,3-dipolar cycloaddition reaction. However, the stereochemistry of bispirooxindoles have not yet been determined when applying cyclic amino acids.[11] The reactivities of this 1,3-dipolar cycloaddition reaction to construct bispirooxindoles still need to be carefully and systematically studied, and the relative configuration of many of them still need to be resolved. In this paper, we wish to report a highly regio- and stereoselective synthesis of densely functionalized bispirooxindole analogues via a three-component 1,3-dipolar cycloaddition reaction of in situ generated azomethine ylides from isatin and proline to different electron-deficient trisubstituted cyclic olefins under mild conditions.
Results and Discussion

Initial examination was carried out using N-benzyl-protected isatin 1a (0.1 mmol), l-proline (0.12 mmol) and (E)-ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate 2a (0.12 mmol) as the substrates in methanol at 60 °C for 2 h to determine the reaction outcome (Table 1, Entry 1). We found that the desired cycloadduct 3a was obtained in 67 % yield with >99:1 diastereomeric ratio (d.r.). Subsequently, we attempted to optimize the reaction conditions by screening solvents, and the results are summarized in Table 1 (Entries 2–5). As depicted in Table 1, the employed solvent had a significant influence on the reaction outcome. Using acetonitrile or toluene as the solvent, the yield of desired product 3a decreased to 51 % or 20 %, respectively (Entries 2, 3). The reaction could not take place in acetone (Entry 4). Using ethanol as the solvent, the yield of 3a was increased to 96 % along with excellent diastereoselectivities (Entry 5). Therefore, ethanol was the most suitable solvent for this reaction. Lowering the reaction temperature to 50 °C, 40 °C, 30 °C or room temperature (20 °C), the reaction proceeded smoothly, and the yield of 3a slightly decreased to 92 % (Table 1, Entries 6–9). The stereochemistry of 3a were determined by X-ray analysis and the ORTEP drawing is presented in Figure 2A (CIF data are summarized in the Supporting Information).

With the identification of the optimal reaction conditions, the generality of this three-component 1,3-dipolar cycloaddition reaction was examined using a variety of isatines 1 and isatin-derived electron-deficient alkenes 2. The results are summarized in Table 2. All reactions proceeded smoothly to give the corresponding products 3 in moderate to good yields with excellent stereoselectivities under the optimal conditions (Table 2). Good yields and excellent stereoselectivities were obtained when utilizing electron-deficient oxindole alkenes 2b–f as the substrates because regardless of whether R3 is an electron-donating or -withdrawing substituent on the aromatic ring, the reactions proceeded smoothly to

![Scheme 1](image1)

**Scheme 1.** The reaction model of the decarboxylative condensation of isatin with different amino acid.

| Table 1. Optimization of the reaction conditions of the three-component 1,3-dipolar cycloaddition. |
|---|
| Entry\[a\] | Solvent | T [°C] | d.r. \[^{[b]}\] | Yield [%]\[^{[c]}\] |
| 1 | MeOH | 60 | >99:1 | 67 |
| 2 | Actone | 60 | – | trace |
| 3 | CH3CN | 60 | >99:1 | 51 |
| 4 | Toluene | 60 | >99:1 | 20 |
| 5 | EtOH | 60 | >99:1 | 96 |
| 6 | EtOH | 50 | >99:1 | 96 |
| 7 | EtOH | 40 | >99:1 | 92 |
| 8 | EtOH | 30 | >99:1 | 92 |
| 9 | EtOH | 20 | >99:1 | 92 |

[a] All reaction was carried out with 1a (0.1 mmol), l-proline (0.12 mmol), 2a (0.1 mmol) in solvent (1.0 mL) in 2 h; [b] Determined by 1H NMR spectroscopy; [c] Isolated yield.

![Figure 2](image2)

**Figure 2.** The X-ray crystal structures of 3a and 5g.
Table 2. Substrate scope of the three-component 1,3-dipolar cycloaddition reaction of 1, l-proline and 2.

| Entry[a] | 1 [R1/R2] | 2 [R3/R4] | d.r.[b] | 3 Yield [%][c] |
|----------|------------|------------|---------|---------------|
| 1        | 1a (H/Bn)  | 2b (5-CH3/Bn) | >99:1   | 3b: 87        |
| 2        | 1a (H/Bn)  | 2c (7-CH3/Bn) | >99:1   | 3c: 90        |
| 3        | 1a (H/Bn)  | 2d (6-OCH3/Bn) | >99:1   | 3d: 69        |
| 4        | 1a (H/Bn)  | 2e (7-OCH3/Bn) | >99:1   | 3e: 72        |
| 5        | 1a (H/Bn)  | 2f (5-Cl/Bn)  | >99:1   | 3f: 81        |
| 6        | 1b (5-CH3/Bn)[d] | 2a (H/Bn)  | >99:1   | 3g: 72        |
| 7        | 1c (6-CH3/Bn)[d] | 2a (H/Bn)  | >99:1   | 3h: 68        |
| 8        | 1d (7-CH3/Bn)[d] | 2a (H/Bn)  | >99:1   | 3i: 73        |
| 9        | 1e (5-F/Bn) | 2a (H/Bn)  | >99:1   | 3j: 81        |
| 10       | 1f (5-Br/Bn) | 2a (H/Bn)  | >99:1   | 3k: 83        |
| 11       | 1a (H/Bn)  | 2g (H/allyl) | >99:1   | 3l: 89        |
| 12       | 1a (H/Bn)  | 2h (H/H)    | >99:1   | 3m: 98        |
| 13       | 1a (H/Bn)  | 2i (H/CH3)  | >99:1   | 3n: 87        |
| 14       | 1g (H/CH3) | 2a (H/Bn)  | >99:1   | 3o: 83        |
| 15       | 1h (H/9-anthmethyl)[d] | 2a (H/Bn)  | >99:1   | 3p: 85        |
| 16       | 1i (H/allyl) | 2j (H/allyl) | >99:1   | 3q: 99        |
| 17       | 1j (4-Br/Bn) | 2a (H/Bn)  | –       | NR[d]         |

[a] All reactions were carried out with 1 (0.1 mmol), l-proline (0.12 mmol), 2 (0.1 mmol) in ethanol at 50 °C. [b] Determined by crude product 1H NMR analysis of crude products. [c] Isolated yield by column chromatography. [d] NR = no reaction.

give the corresponding bispirooxindole products 3b–f in good yields (69–90%) with excellent stereoselectivities (single isomer) (Table 2, Entries 1–5). Meanwhile, different substituents on the aromatic ring of isatin 1 did not impact the yield of 3 significantly (Table 2, Entries 6–10). Substrates with electron-donating substituent on the aromatic ring of isatins produced 3 in moderate yields (68–73%) upon prolonging the reaction time to 24 h (entries 6–8). The yields of 3 decreased slightly using substrates with electron-withdrawing substituents on the aromatic ring (Entries 9–10). Experiments with different protecting groups at the nitrogen atoms of 1 or 2 were also conducted. To our delight, with these different protecting groups such as allyl, methyl, 9-anthracenemethyl or without protecting group, the reactions proceeded efficiently, affording the corresponding products in 73–99% yield with >99:1 d.r. (Entries 11–16). It should be noted that using isatin 1k having a R1 substituent at the C4 position, the three-component 1,3-dipolar cycloaddition could not give the corresponding product, perhaps due to a steric effect (Table 2, Entry 17).

Instead of 2, we next attempted to use various isatin-derived electron-deficient alkenes 4 to examine the reaction outcome. Gratefully, we found that the reactions also proceeded smoothly to give the annulation products in high yields with high diastereoselectivities. The results are summarized in Table 3. Changing the electron-withdrawing group to an acetyl group, the reaction was also tolerant to an electron-deficient or electron-rich aromatic ring of 4a–e (R2 = H, 6-Br, 7-Br, 5-Cl or 5-CH3) with 1a and l-proline, providing a series of the desired products 5a–e in 75–93% yields with excellent diastereoselectivities (Table 3, Entries 1–5). Switching the electron-withdrawing group to benzoyl, cyano, benzyl ester or a phenyl group, the corresponding products were obtained in 80–99% yields (Table 3, Entries 6–9). The stereochromical outcome of this cycloaddation was determined by single-crystal X-ray analysis of bispirooxindole 5g. The ORTEP drawing is shown in Figure 2B ( CIF data are summarized in the Supporting Information).

We also investigated L-pipelic acid or sarcosine instead of L-proline in this reaction. The desired bispiro product could be obtained in almost quantitative yield with single stereoisomer (up to 99% yield and >19:1 d.r.), respectively (Scheme 2A and 2B). Enlarging the reaction scale to 5.0 mmol afforded 3a and 5g in 92% and 90% yields, respectively, under the standard conditions (Scheme 2B).

Subsequently, we applied electron-deficient alkenes 8, which have similar structural motifs as 4, in this three-component 1,3-dipolar cycloaddition reaction. The results are summarized in Scheme 3. Regardless of whether R1 or R2 is an electron-rich or electron-deficient aromatic ring, the reactions proceeded smoothly to give the 3-[4-e] annulation products in 75–94% yields along with >99:1 d.r. values (Scheme 3). The stereochromies of compounds 9 have not yet been determined, since these compounds gradually decomposed during recrystallization.

We next utilize this methodology to alkene 10 derived from piperidine and alkyldiene azlactone 12. As results, the corresponding products 11 were obtained in 92% and 67% yields as single stereoisomer, respectively (Scheme 4A and 4B). The

Table 3. Substrate scope of the three-component 1,3-dipolar cycloaddition reaction of 1a, l-proline and 4.

| Entry[a] | 4 [EWG/R5/R6] | d.r.[b] | 5 Yield [%][c] |
|----------|----------------|---------|---------------|
| 1        | 4a (COCH3/H/Bn) | >99:1   | 5a: 93        |
| 2        | 4b (COCH3/5-CH3/Bn) | >99:1   | 5b: 83        |
| 3        | 4c (COCH3/6-Br/Bn) | >99:1   | 5c: 75        |
| 4        | 4d (COCH3/7-Br/Bn) | >99:1   | 5d: 78        |
| 5        | 4e (COCH3/5-Cl/Bn) | >99:1   | 5e: 82        |
| 6        | 4f (COPh/5-F/Bn)  | >99:1   | 5f: 99        |
| 7        | 4g (CN/H/Bn)     | >99:1   | 5g: 91        |
| 8        | 4h (CO/BN/H/Bn)  | >99:1   | 5h: 84        |
| 9        | 4i (Ph/H/H)      | >99:1   | 5i: 80        |

[a] All reaction was carried out with 1a (0.1 mmol), l-proline (0.12 mmol), 2a (0.1 mmol) in ethanol (1.0 mL) for 2 h. [b] Determined by crude product 1H NMR spectroscopy. [c] Isolated yield by column chromatography.

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stereochemistry of bispiro compound 11 has been determined by single-crystal X-ray analysis and its ORTEP drawing is indicated in Figure 3.

Conclusions

In conclusion, we have synthesized a series of bispirooxindole compounds via a three-component 1,3-dipolar cycloaddition reaction with respect to a variety of different alkenes, affording the corresponding bispirooxindoles in moderate to good yields (up to >99%) and excellent diastereoselectivities (as single isomer in most cases) under mild conditions. Current efforts focusing on the asymmetric version of this reaction and applying this methodology to synthesize biologically active products are also in progress.

Experimental Section

General procedure: Isatin 1 (0.10 mmol), L-proline (0.12 mmol) and electron-deficient olefin (0.1 mmol) were added to a reaction tube. Ethanol (1.0 mL) was added, and the resulting reaction mixture was stirred at RT for 2–48 h. The solvent was removed under reduced pressure and residue was chromatographed on silica gel (elution with petroleum ether/EtOAc = 6:1–4:1) to provide the desired product or filtrated to get the product.

Ethyl 2,3-bis(1′-benzyl-spiro-3′-indolino)-hexahydro-1H-pyrrolizine-1-carboxylate (3a): White solid (57 mg 96%): mp: 151–152°C; 1H NMR (400 MHz, CDCl3, TMS): δ = 7.69 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.14–6.87 (m, 10 H), 6.69 (d, J = 6.8 Hz, 2 H), 6.50 (d, J = 6.8 Hz, 2 H), 5.28–5.23 (m, 1 H), 4.91 (d, J = 16.0 Hz, 1 H), 4.89 (d, J = 16.0 Hz, 1 H), 4.48 (d, J = 16.0 Hz, 1 H), 4.21 (d, J = 16.0 Hz, 1 H), 3.88 (m, J = 10.0 Hz, 1 H), 3.79–3.71 (m, 1 H), 3.68–3.55 (m, 2 H), 2.92 (d, J = 8.4 Hz, 2 H), 2.92 (m, J = 11.0 Hz, 1 H), 1.94–1.88 (m, 1 H), 0.55 (t, J = 8.0 Hz, 3 H); 13C NMR (100 MHz, CDCl3): δ = 177.2, 175.2, 143.5, 142.9, 135.2, 129.6, 128.7, 128.6, 128.5, 127.7, 127.1, 127.0, 126.6, 126.4, 126.3, 122.5, 122.1, 109.0, 108.5, 77.9, 67.1, 66.6, 60.3, 57.9, 48.1, 43.8, 43.4, 29.7, 26.0, 13.4; IR (neat) ν = 3064, 1729, 1703, 1607, 1487, 1361, 1178, 1113, 1015, 761.
Scheme 4. [3+2] Annulation of A) olefin 10 and B) olefin 12.

Figure 3. The X-ray crystal structure of 11.

694 cm⁻¹; MS (ESI): m/z (%): 598.4 (100) [M + H]⁺; HRMS: m/z [M + H]⁺ calcd for C₁₉H₂₁N₃O₄: 598.2708, found: 598.2700.

Spectroscopic data of the compounds shown in Tables 1–3 and Scheme 1–3, the detailed descriptions of experimental procedures and the crystal structures of 3a, 5g, 8c and 11 are given in the Supporting Information. CCDC-821930 (3a), CCDC-824511 (5g), CCDC-826476 (8c) and CCDC-863229 (11) contain 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.

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