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New Synthetic Route to Substituted Tetracenes and Pentacenes via Stereoselective [4+2] Cycloadditions of 1,4-Dihydro-1,4-epoxynaphthalene and Isobenzofuran

Shohei Eda, Fumiaki Eguchi, Hiroshi Haneda, and Toshiyuki Hamura*

Stereoselective [4+2] cycloadditions of 1,4-dihydro-1,4-epoxynaphthalene and isobenzofuran were described. Among several possibilities, syn-exo and/or anti-endo isomers were selectively produced depending on the substitution pattern of the reactants. Importantly, the syn-exo isomer underwent acid promoted aromatization, affording the corresponding tetracene. These findings enabled us to prepare a substituted pentacene with electron withdrawing groups.

Due to the inherent strain, 1,4-epoxynaphthalenes show potentially interesting reactivities in organic syntheses. The [4+2] cycloaddition of I with dienes is one of their representative reactions for construction of polycyclic compounds. Among various dienes, isobenzofuran II, a 10π electron system, is an attractive reactive partner of I, since it can readily cyclize with I to give diepoxytetracene III, which can be viewed as an efficient precursor to substituted tetracenes (Scheme 1). However, conversions of III to tetracenes IV was reported to be unsuccessful, resulting in the formation of ring cleaved products. These unfortunate results discouraged the syntheses of various functionalized derivatives of III.

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Table 1 shows the initial model reaction. Upon heating of epoxynaphthalene I and diphenylisobenzofuran II in toluene at 110 °C, the [4+2] cycloaddition occurred smoothly to give the cycloadduct 3 in 96% yield (entry 1). In this case, syn-exo isomer 3aA was selectively obtained as a major product, accompanied by a small amount of the anti-endo isomer 3aB. Same reaction performed at lower reaction temperature slightly improved the syn-exo selectivity, although the prolonged reaction time was required to consume the starting material (entries 2 and 3). Use of another solvents showed little effect (entries 4–8).

These observed stereoselectivity is due to the concave topology of the epoxynaphthalene I, which would force the isobenzofuran to approach along the convex side of I. The stereochemistry of each cycloadduct was determined by X-ray analysis (Figure 1). These cycloadducts were thermally stable.
and retro Diels–Alder reaction did not occur at all under the reaction conditions (toluene, 110 °C).

Table 1 Initial model study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield (%)</th>
<th>3aA : 3aB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>110</td>
<td>0.5 h</td>
<td>96</td>
<td>75 : 25</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>25</td>
<td>8 h</td>
<td>86</td>
<td>79 : 21</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>0</td>
<td>8 d</td>
<td>83</td>
<td>81 : 19</td>
</tr>
<tr>
<td>4</td>
<td>benzene</td>
<td>80</td>
<td>3 h</td>
<td>95</td>
<td>77 : 23</td>
</tr>
<tr>
<td>5</td>
<td>hexane</td>
<td>69</td>
<td>3.2 h</td>
<td>93</td>
<td>76 : 24</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CN</td>
<td>82</td>
<td>3.5 h</td>
<td>94</td>
<td>67 : 23</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>78</td>
<td>2 h</td>
<td>96</td>
<td>76 : 24</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>65</td>
<td>3.5 h</td>
<td>95</td>
<td>77 : 23</td>
</tr>
</tbody>
</table>

*1.2 equiv of 1 and 1.0 equiv of 2a. Syn and anti represent the relative relationship between the two oxygen bridges.

Table 2 [4+2] cycloaddition of epoxynaphthalene and isobenzofuran

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Ar</th>
<th>R¹</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>H</td>
<td>F</td>
<td>3b</td>
<td>94 (75 : 25)³</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>H</td>
<td>OMe</td>
<td>3c</td>
<td>95 (76 : 24)³</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>H</td>
<td></td>
<td>3d</td>
<td>82 (80 : 20)³</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>F</td>
<td></td>
<td>3e</td>
<td>87 (57 : 43)³</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>Cl</td>
<td></td>
<td>3f</td>
<td>97 (68 : 32)³</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>OMe</td>
<td></td>
<td>3g</td>
<td>98 (76 : 24)³</td>
</tr>
</tbody>
</table>

*The reaction was performed for 30 h. Syn-exo : anti-endo.

This [4+2] cycloaddition could be applicable to various substrate combinations. Upon heating of epoxynaphthalene 1 with diarylisobenzofurans 2b and 2c, having a fluoro or a methoxy group on the aromatic ring at para position (toluene, 110 °C, 0.5 h), the [4+2] cycloadditions occurred stereoselectively to give cycloadducts 3bA and 3cA as major products, respectively (entries 1 and 2). Isobenzofuran 2d, having a sterically congested o-tolyl group, cyclized slowly with 1 (110 °C, 30 h) to give cycloadduct 3d in 82% yield (entry 3).

Furthermore, substituents at C₅ and C₆ position on the isobenzofuran slightly influenced the stereoselectivity. The cycloadditions of isobenzofurans 2f and 2g, having a chloro or methoxy group, with 1 occurred smoothly to give the cycloadducts 3f and 3g with moderate stereoselectivities (entries 5 and 6). On the other hands, the corresponding reaction of fluoride 2e resulted in the poor selectivity (entry 4).

Further investigation revealed that introduction of the substituent at C₁ and C₄ position in epoxynaphthalene switched the stereoselectivity (Scheme 2). Upon treatment of epoxynaphthalene 1 with tetraine 4 in toluene at 50 °C, isobenzofuran 5 was generated, which was intercepted by 1,4-diphenylepoxynaphthalene 6 to give anti-endo isomer 3aC as a major stereoisomer (3aA/3aC = 2 : 3). Remarkably, heating of 1,4-diphenylepoxynaphthalene 6 and diphenylisobenzofuran 2a in toluene at 110 °C gave anti-endo isomer 7 as an exclusive product, whose stereochemistry was unequivocally confirmed by X-ray analysis.¹⁰,¹¹

Scheme 2 Stereoselective [4+2] cycloaddition of 1,4-disubstituted epoxynaphthalene.
We next focused our attention to the conversion of [4+2] cycloadducts to the corresponding tetracenes (Scheme 3). All attempts on acid promoted aromatization of anti-endo isomers 3B to the corresponding tetracenes have failed. In these cases, however, ring cleavage occurred predominantly. For example, treatment of 3aB with TsoH (toluene, 80 °C, 1.5 h) gave the phthalaldehyde 8 and diphenylnaphthalene 9 in 33% and 33% yields, respectively (Eq. 1). In sharp contrast, we were pleased to find that the syn-exo isomer 3aA could be cleanly aromatized under the same reaction conditions, affording substituted tetracene 10 in 87% yield (Eq. 2).

A possible reaction course of the [4+2] cycloadducts 3aA and 3aB to the ring cleaved or the aromatized products 8–10 is shown in Scheme 4.

The formation of the ring cleaved products 8 and 9 can be explained by Grob type fragmentation, since the anti orientation of the two epoxide bridges in the protonated intermediate A would facilitate the cleavage of the carbon–carbon bond a and the carbon–oxygen bond b with an anti-periplanar relationship. The intermediate B, thus formed, underwent the nucleophilic addition of water, and subsequent proton transfer and fragmentation of the resulting lactol D gave the phthalaldehyde 8 and 1,4-diphenylnaphthalene 9.

On the other hand, the conversion of 3aA to the tetracene 10 is ascribed to the anti orientation of the two protons on the bridge-head carbon with respect to the two epoxide bridges in 3aA, which would facilitate the dehydration of the protonated intermediate E, affording the epoxytetracene G. Second acid induced aromatization of the epoxytetracene G led to the clean formation of the tetracene 10.

Lastly, an important point to emphasize is that this synthetic method could be applied to the synthesis of a substituted pentacene (Scheme 5). Starting from dibromoisobenzofuran 2h, served as a synthetic equivalent of didehydroisobenzofuran H, the precursor of pentacene was rapidly constructed by successive [4+2] cycloadditions. Thus, the first [4+2] cycloaddition of epoxynaphthalene 1 and isobenzofuran 2h smoothly gave cycloadduct 3hA in high yield. In this case, syn-exo isomer was again a major stereoisomer. The second [4+2] cycloaddition of benzene, generated by treatment of syn-exo isomer 3hA with n-BuLi, and furan afforded the [4+2] cycloadduct 11. Subsequent cyanation through the generation of isobenzofuran I by treatment of 11 with tetrazine 4 and its trapping with fumaronitrile gave the product 12 in 89% yield. The cycloadduct 12, thus obtained, was converted to the corresponding tetaepoxypentacene 13 under the basic conditions (LiI, DBU, THF, 65 °C). Final acid-promoted aromatization of 13 under the above mentioned conditions, however, was not satisfied, affording the pentacene 14 only in 12% yield. Re-investigation of the aromatized conditions revealed that Lewis-acid promoted conditions (AlBr3, CsI, CHCl3, 0 °C) improved the yield of the desired product 14.

In summary, stereoslective [4+2] cycloaddition of epoxynaphthalene and isobenzofuran allowed rapid construction of highly functionalized diepoxytetracenes, which were amenable to selective transformation en route to substituted tetracene and pentacene derivatives. Further
synthetic applications are under active investigation in our laboratories. This work was supported by the MEXT and JST, ACT-C. The authors thank Prof. Hidehiro Uekusa (Tokyo Institute of Technology) for X-ray analysis.

Notes and references

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4 To the best of our knowledge, only one example is reported for acid-induced aromatization of dipropoxytetracene to corresponding tetracene derivatives. In this case, the stereochemistry of the starting material was not determined; see: T. E. Youssef and M. Hanack, J. Porphyryns and Phthalocyanins, 2002, 6, 571.


9 For preparation of isobenzofurans, see supporting information. See also ref. 5a and 6.

10 For details, see supporting information.

11 The [4+2] cycloaddition of 1,4-dimethylepoxynaphthalene and diphenylisobenzofuran 2a also gave the corresponding anti-endocycloadduct as a single stereoisomer.


14 The reducing agent that is responsible for producing 10 from the epoxytetracene G, which is probably produced as an initial product, is yet to be identified. See also ref. 8.


17 The same reaction of 3aA by treatment with AlBr3 and CsI gave the tetracene 10 in 51% yield.