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Domino Cyclodimerization of Indole-Derived Donor–Acceptor Cyclopropanes: One-Step Construction of the Pentaleno[1,6-*a*,*b*]indole Skeleton

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Bisindoles represent an extensive group of both naturally occurring and synthetically available compounds with a broad range of biological activities, such as antitumor, antiviral, and antibacterial activities.[1] To date, over 200 bisindole alkaloids have been isolated from various natural sources[2] (Figure 1). Furthermore, considerable attention is currently being paid to the development of synthetic routes to bisindoles. Structurally, bisindoles vary significantly, resulting in a lack of general methods for the synthesis of these compounds, although, most synthetic approaches are based on the coupling of two indole-containing molecules.[3]

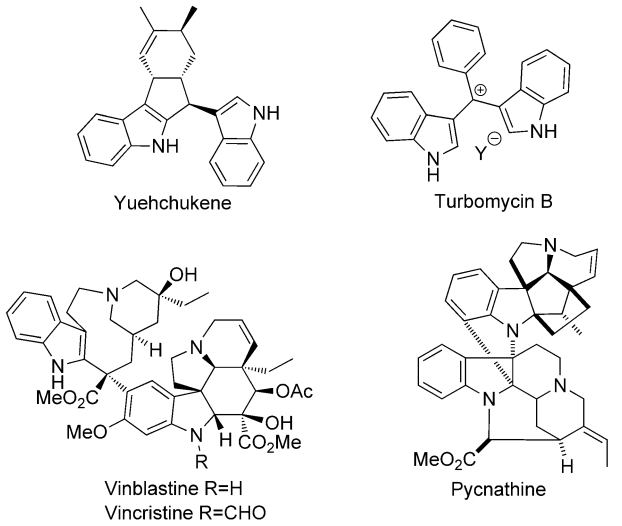

Figure 1. Examples of biologically active bisindole alkaloids.

Herein, we report a new synthetic strategy towards bisindoles through an interaction of two indole-derived donor–acceptor (DA) cyclopropane molecules. DA cyclopropanes are of particular interest because they are promising synthetic reagents with versatile reactivity.[4] In particular, DA cyclopropanes with aryl and heteroaryl substituents are widely used for the synthesis and modification of various indole-containing molecules.[5–7] In this study, we investigate in detail the dimerization of indole-containing DA cyclopropanes and present evidence for a new type of reactivity of DA cyclopropanes, which opens up routes to a novel bisindole scaffold.

Coupling of DA cyclopropanes has received very little attention in the literature, with only one report thus far, which deals with the transformation of aryl 2-(3-indolyl)cyclopropyl ketones into cyclopentacarbazoles.[8] As part of our investigation into DA cyclopropane dimerization,[9] we studied the Lewis acid induced transformation of 2-(3-indolyl)cyclopropane-1,1-dicarboxylates (**1**). We found that this reaction yields angularly fused tetracyclic compounds **2**, containing the previously unknown pentaleno[1,6a–b]indole scaffold. Reagent cyclopropanes **1** are readily available from the corresponding indole-3-carbaldehydes through a standard synthetic sequence of Knoevenagel/Corey–Chaykovsky reactions.[10] These cyclopropanes have low stability at elevated temperatures and on silica gel, but can be isolated as pure materials by chromatography on neutral alumina. *N*-Benzylindoles **1** were found to be more stable during storage than their *N*-methyl analogues.

To find the optimal conditions for the Lewis acid induced DA cyclopropane dimerization, we selected cyclopropane **1a** as a model substrate. Building on a previous study of the related indole-substituted DA cyclopropanes,[8] we started by using the $SnCl_4/CH_3NO_2$ system as the reaction initiator (Table 1). It is noteworthy that the reaction without Lewis acid leads to complete destruction of **1a** into a mixture of polymeric and ring-opened byproducts (Table 1, entry 1). If

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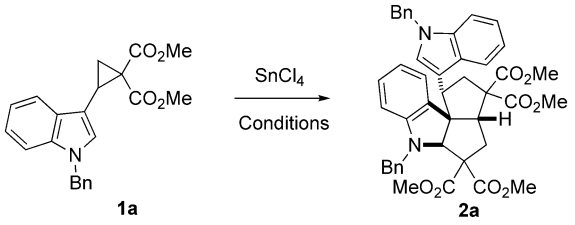
Table 1. Optimization of reaction conditions for the cyclodimerization reaction of **1a**.



1a **2a**

Entry	$SnCl_4$ [mol%]	Conditions Solvent	T [°C]	t [h]	Yield [%][a]
1	–	CH_3NO_2	101	12	–[b]
2	50	CH_3NO_2	20	4	–[c]
3	120	CH_3NO_2	20	4	–[c]
4	120	CH_3NO_2	60	2	67
5	190	CH_3NO_2	70	3	21
6	120	CH_2Cl_2	42	3	55
7	120	C_6H_6	80	1	25

[a] Isolated yield. [b] Unidentified products. [c] Lactone **3** was the only isolated product (78% yield).

the reaction was performed in the presence of $SnCl_4$ at room temperature, cyclopropane **1a** yielded only lactone **3**[11] (Table 1, entries 2 and 3). This lactone formation is typical for the Lewis acid induced transformation of cyclopropane-1,1-diesters.[12] In this case, variation of the quantity of Lewis acid had no effect on the reaction results. However, increasing the reaction temperature led to the formation of dimeric product **2a**. The best yield of **2a** was obtained if the reaction was performed at 60°C in the presence of 120 mol% of $SnCl_4$ (Table 1, entry 4). Under these conditions **2a** was formed as a single low-molecular weight product in 67% yield. Any further increase in the temperature, variation of the Lewis acid loading or change to a low-polar or non-polar solvent (CH_2Cl_2, benzene) resulted in diminished yields of **2a** (Table 1, entries 5–7).

Compound **2a** is formed as a single diastereomer. Its structure was assigned by use of 1D and 2D COSY, HETCOR, HMBC, and NOESY NMR spectral data. Several criteria were used to elucidate the structure of **2a**: 1) the presence of double the number of resonances in the ^{13}C NMR spectrum points to **2a** being a dimer of **1a**; 2) the presence of two ABX systems for the protons of two isolated CH–CH_2 fragments in the ^1H NMR specrum, which, according to the HMBC spectrum, are connected to the different $C(CO_2Me)_2$ groups; 3) the main characteristics of an indoline system are two signals at $\delta_C = 66$ and 77 ppm, which were assigned, respectively, to the quaternary C10b and tertiary C5a atoms; and 4) the presence in the aromatic region of only one set of signals for 3-substituted indole, whereas the indoline system is represented by resonances corresponding to a disubstituted benzene ring. The relative stereochemistry of **2a** was deduced from its NOESY spectrum. The central pentaleno[1,6a–b]indole core has the only possible relative configuration, whereas the indolyl substituent at the C1 atom is arranged in a *trans* position relative to the indoline core (Figure 2).[13]

With the optimized conditions in hand, we investigated the scope of this new domino reaction by using a series of cyclopropanes **1b–i** (Table 2). Cyclopropanes **1a–g** are readily transformed into the corresponding dimers **2a–g** as single diastereomers in good yields (Table 2, entries 1–7). Thus, this dimerization was found to be a generally applicable reaction for *N*-alkylindoles **1**. However, the presence of an acceptor substituent on N1 (**1i**) or even a small substituent on C2 of the indole moiety in **1** (**1h**) prevented formation of the desired products (Table 2, entries 8 and 9). The structure and relative stereochemistry of dimers **2b–g** were established by use of spectroscopic data, which are similar to those of **2a**. The structure of cyano-derivative **2f** has been unambiguously proven by single-crystal X-ray analysis.[14]

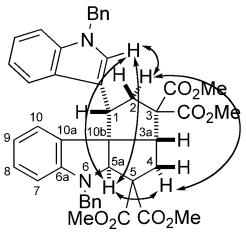
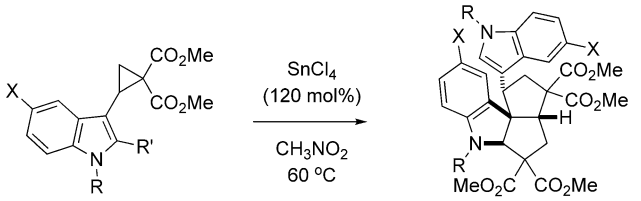


Figure 2. Representative NOE spectrum enhancements for **2a**.

Table 2. Cyclodimerization of cyclopropanes **1** to form tetracyclic compounds **2** (Bn = benzyl, Ts = tosyl).

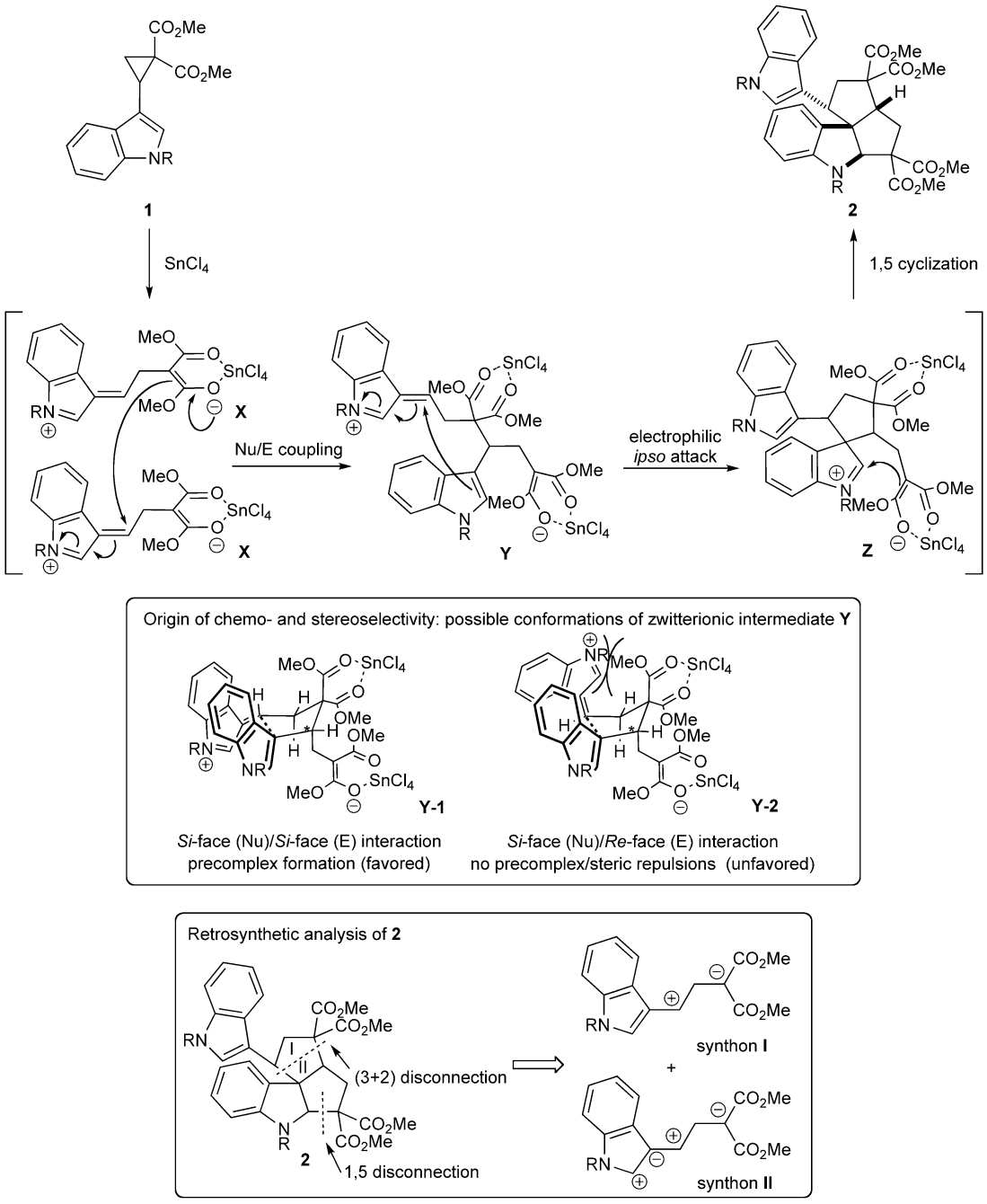


1a–i **2a–g**

Entry	Reagent	R	R′	X	T [h]	Product	Yield [%][a]
1	**1a**	Bn	H	H	2	**2a**	67
2	**1b**	Me	H	H	2.5	**2b**	64
3	**1c**	Bn	H	F	2	**2c**	75
4	**1d**	Bn	H	Cl	2	**2d**	68
5	**1e**	Me	H	Br	3	**2e**	71
6	**1f**	Bn	H	CN	2	**2f**	68
7	**1g**	$(CH_2)_3Ph$	H	H	2.5	**2g**	57
8	**1h**	Bn	Me	H	2	**2h**	–
9	**1i**	Ts	H	H	2	**2i**	–

[a] Isolated yield.

A possible mechanism for the cyclodimerization of **1** to form **2** is shown in Scheme 1. The presence of a strong Lewis acid in a polar solvent, such as nitromethane, induces the cyclopropane ring-opening reaction, affording zwitterionic intermediate **X**. In contrast, moderately activating Lewis acids in low-polar solvents usually give rise to intimate-ion-pair formation.[15,16] The coupling of electrophilic and nucleophilic centers of two intermediates **X** yields dimeric zwitterionic intermediate **Y**. This step is analogous to the first step in the dimerization of 2-(indolyl)cyclopropyl ketones.[8] However, the next step is dramatically different; attack of the electrophilic center in **Y** on C3 of the indole ring occurs to give zwitterionic intermediate **Z**.[17] Finally, interaction of the malonyl anion fragment with the cationic



Scheme 1. A possible mechanism for the formation of pentaleno[1,6a–b]indoles **2**.

center at C2 of the indole ring affords an angularly fused pentaleno[1,6a–b]indole.

The stereochemical outcome of this reaction is defined during the transformation of **Y** into **Z** and can be explained in terms of the possible conformations of zwitterion **Y** before the electrophilic *ipso* attack (Scheme 1). The favorable **Y-1** conformation is stabilized by orbital overlap between the two indole moieties, one of which is electron poor due to conjugation with the cationic center. This overlap leads to the formation of a π–π* donor–acceptor precomplex.[18] Electrophilic *Si*-face attack onto the *Si* face of the nucleophile followed by cyclization results in the formation of **2**. The alternative electrophilic *Re*-face attack onto the *Si* face of the nucleophile (**Y-2**), leading to the C1 epimer of **2**, does not occur due to the reduced orbital overlap and higher steric repulsion in **Y-2** relative to **Y-1**. Remarkably, the chemo- and regioselectivity of the formation of **2** can also be explained by the formation of a π–π* precomplex leading to close proximity of the original benzylic cation and the indole C3 atom.

This transformation is a unique domino cyclodimerization reaction in which one molecule of cyclopropane reacts as a

synthetic equivalent of 1,3-zwitterionic synthon **I** and the second molecule enters the reaction as a synthetic equivalent of unusual synthon **II** (Scheme 1). The reactivity as synthon **I** is typical for DA cyclopropanes,[4–7] whereas the reactivity as synthon **II** has not so far been described.

We have also investigated the antitumor activity of the synthesized pentaleno[1,6a–b]indoles **2**. Despite low solubility, all of the compounds studied demonstrate low-to-moderate cytotoxicity towards HeLa cancer cells.[11]

In conclusion, we have discovered a domino reaction of readily available 2-(3-indolyl)cyclopropane-1,1-diesters that produces cyclic dimers with the pentaleno[1,6a–b]indole scaffold. During this cyclodimerization reaction, the formation of two rings, three C–C σ bonds and four stereogenic centers occurs with exceptionally high chemo-, regio-, and stereoselectivity. In this reaction the DA cyclopropanes demonstrate a conceptually new type of reactivity with participation of four reaction sites: two nucleophilic (the C1 atom of the cyclopropane ring and the C2 atom of indole) and two electrophilic (the C3 atom of the cyclopropane ring and the C2 atom of indole) centers. This new kind of DA cyclopropane reactivity might also be observed for other substrates with (hetero)aromatic substituents that are prone to *ipso* attack. An investigation into these transformations and a further study into the physiological activities of compounds **2** are currently in progress.

Experimental Section

General procedure for synthesis of dimers 2a–g: A solution of $SnCl_4$ (0.15 mL, 1.26 mmol) in dry nitromethane (2 mL) was added to a solution of cyclopropane **1** (1 mmol) in nitromethane (15 mL) that contained activated molecular sieves (4 Å) at room temperature under an argon atmosphere. The flask containing the resulting mixture was placed in an oil bath and heated to 60 °C. The mixture was stirred for 2–3 h, poured into saturated aqueous $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), and saturated aqueous Trilon B (10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (SiO_2) afforded compounds **2**.

Acknowledgements

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Keywords: cyclopropanes · dimerization · domino reactions · donor–acceptor systems · indoles · Lewis acids

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