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SYNTHESIS OF PHENANTHROLINE AND INDOLE BASED HYBRID CYCLOPHANE DERIVATIVES VIA RING-CLOSING METATHESIS[†]

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[†] This paper is dedicated to Prof. Dr. Lutz F. Tietze on the occasion of his 75th birthday.

Abstract – Here, we report new phenanthroline-based cyclophane derivatives via Fischer indolization and ring-closing metathesis (RCM) as key steps. Addition of Grignard reagent to 1,10-phenanthroline-2,9-dicarbaldehyde **2** and subsequent autoxidation gave the bis-alkene dione derivative **3**. Further, Fischer indolization **3** followed by RCM under mild reaction conditions gave indole and containing hybrid cyclophanes such as **6a** and **6b**.

Phenanthroline derivatives are useful in co-ordination chemistry and they act as ligands for binding various metal ions (e.g. Cu, Ru, La, Os and V).[1] Interestingly, phenanthroline-based copper complexes show interesting biological activity towards human cell lines.[2] Herein, we report a simple synthetic approach to cyclophanes which contain phenanthroline and indole moieties. These new cyclophanes may serve as ligands for various metal complexes. Due to this attractive feature several efforts are devoted for the synthesis of phenanthroline-based macrocycles. Synthesis of such macrocycles is a challenging task due to the unfavourable entropy factor and also with the ring strain involved with these systems. Ring-closing metathesis (RCM) is a useful tool to assemble various types of macrocycles which are commonly found in natural products, pharmaceuticals and supramolecular chemistry.[3] Among several available methods for the synthesis of cyclophanes, RCM is a useful option to accomplish a late-stage ring-closure.[4] Recently, we reported several synthetic approaches to cyclophanes via Suzuki-Miyaura cross-coupling, Claisen rearrangement and RCM as key steps.[5,6] Here, we conceived a simple synthetic strategy to phenanthroline-based cyclophane derivatives via a RCM as a key step.

Design and synthesis of cyclophane derivatives[5b] containing heterocycles is considered to be a difficult task. Here, we report a simple synthetic strategy which can provide an easy access to diverse cyclophanes containing indole and phenanthroline moieties in the same molecule. The retrosynthetic analysis to phenanthroline-based cyclophane relies on Fischer indolization and RCM as key steps (Figure 1).

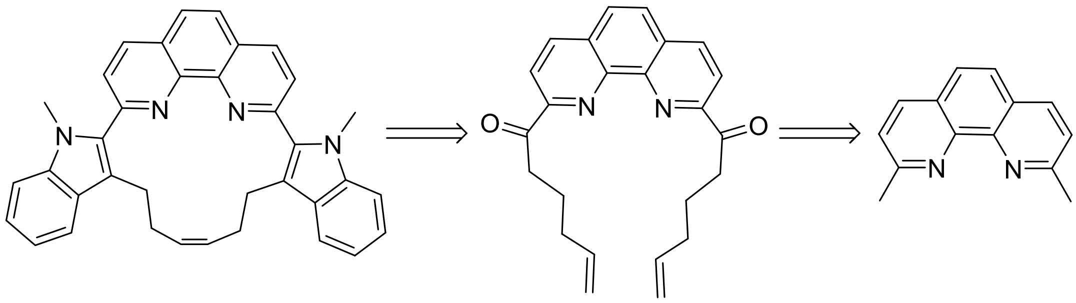
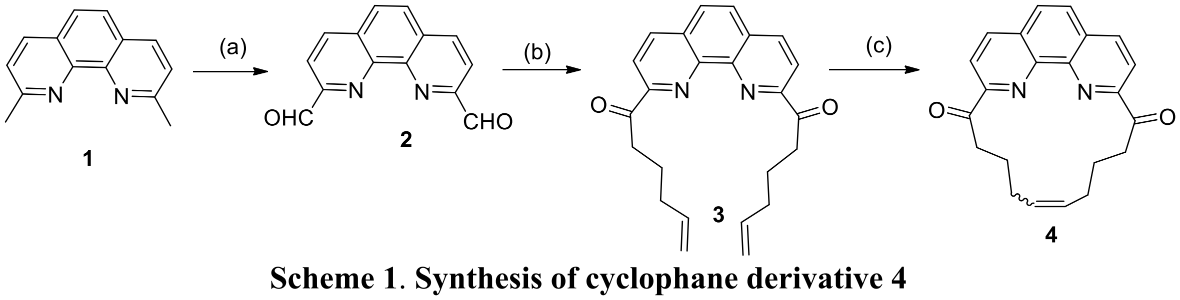


Figure 1. **Retrosynthesis approach to indole and phenanthroline-based hybrid cyclophane derivative**

To begin with, commercially available 2,9-dimethyl-1,10-phenanthroline **1** was oxidized in the presence of SeO_2 to generate the 1,10-phenanthroline-2,9-dicarbaldehyde **2**,[7] which on further reaction with Grignard reagent such as 6-hexenylmagnesium bromide did not give the expected diol, however, interestingly we have isolated the bis-alkene dione **3** (86%). Here, it appears that bis-alkene dione **3** is formed by aerial oxidation. Subsequently, bis-alkene dione **3** was subjected to RCM in the presence of Grubbs second generation catalyst (G-II) in CH_2Cl_2 at room temperature (rt) to deliver the cyclophane derivative **4** as a mixture of *cis* and *trans* isomer and the ratio based on ^{1}H NMR (8:2) (89%). These isomers are not separable by column chromatography because both of them have the same R*f* value (Scheme 1).

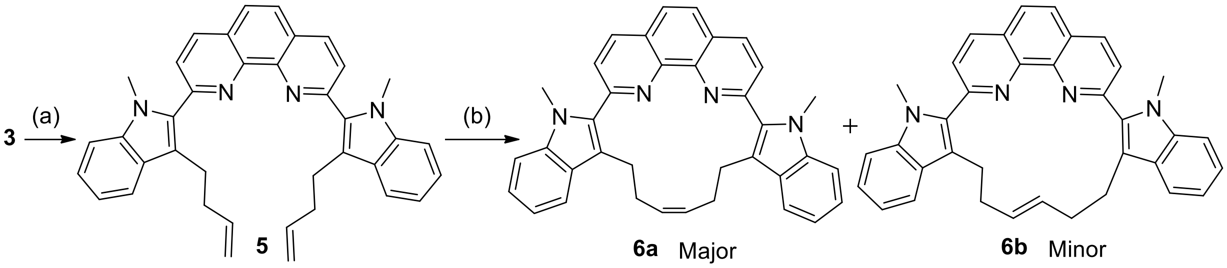


Scheme 1. **Synthesis of cyclophane derivative 4**

Reagents and conditions: (a) SeO_2, DMSO, reflux, 3 h, 63%; (b) Mg, I_2, THF, C_5H_9Br, 6 h, 86%; (c) G-II, CH_2Cl_2, rt, 24 h, 89%.

We are also interested in developing hybrid cyclophanes containing indole and phenanthroline moieties. Therefore, bis-alkene dione **3** was subjected to the Fischer indolization to deliver the bis-indole derivative **5** (89%) under low melting mixture conditions.[8] Later, the compound **5** containing bis-indole moiety with terminal alkene groups was subjected to ring closure in the presence of G-II to deliver the cyclophane derivatives **6a** and **6b**. These cyclophanes were separated by column chromatography and their structures were assigned on the basis of ^{1}H NMR, and ^{13}C NMR spectral data and further supported by HRMS data.

To determine the configuration of the double bond present in **6a** and **6b** (Scheme 2), their single crystal X-ray diffraction data were collected and based on this information the major product was found to be a *cis* isomer and the minor product was a *trans* isomer (Figure 2).



Scheme 2. Synthesis of cyclophane derivative 6a and 6b

Reagents and conditions: (a) L-(+)-tartaric acid:*N, N'*-dimethylurea, $PhNMeNH_2$, 70 °C, 12 h, 89%; (c) G-II, CH_2Cl_2, rt, 24 h, 94%.

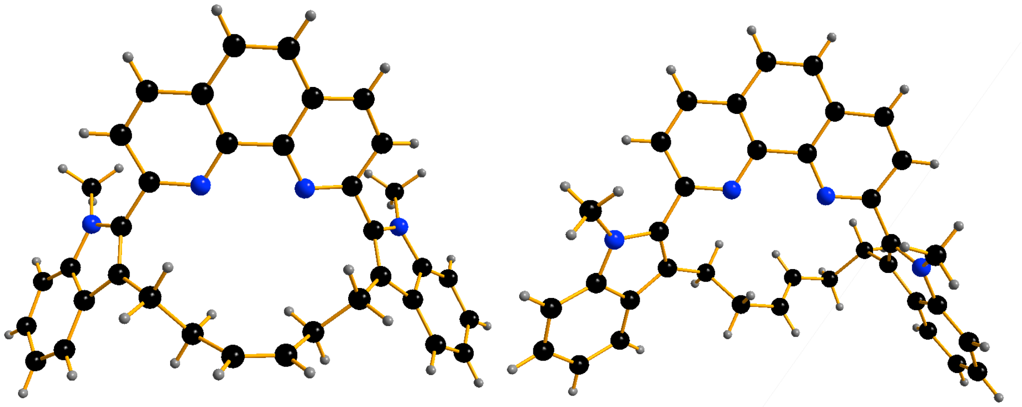


Figure 2. The molecular crystal structure of 6a and 6b[9]

We have developed a simple synthetic methodology to phenanthroline and indole-based hybrid cyclophane derivatives via RCM utilizing G-II catalyst. In both these instance RCM gave a mixture of *cis* and *trans* isomers. Having, inbuilt indole moiety next to the aromatic ring gave the *cis* isomer **6a** as a major product and *trans* isomer **6b** as a minor product during the RCM sequence. Their structures were confirmed by single crystal X-ray diffraction data.

EXPERIMENTAL

All reactions were performed under an argon or nitrogen atmosphere using well-dried reaction flask. All commercially products were used as received without further purification. All the solvents used as reaction media were dried over predried molecular sieves (4 Å) in oven. Column chromatography was performed with silica gel (100-200 mesh) using mixture of petroleum ether and EtOAc as eluent. ^1H and ^{13}C NMR spectral data were recorded on 400 MHz and 100 MHz or 500 MHz and 126 MHz spectrometers using tetramethylsilane (TMS) as an internal standard and chloroform-*d* as a solvent. The high resolution mass spectroscopy (HRMS) was performed using Brucker (Maxis Impact) or Micromass Q-ToF spectrometer. X-Ray diffraction data for compounds **6a** and **6b** were collected on a diffractometer equipped with graphite monochromated Mo Kα radiation. The structure was solved by direct methods shelxs-97 and refined by full-matrix least-squares against F^2 using shelxl-97 software. The melting points recorded are uncorrected.

bis-Alkene dione 3

Mg turnings (139 mg, 5.79 mmol) and iodine in THF (5 mL) were heated to reflux until the brown color disappeared. Then, 5-bromo-1-pentene (273 mg, 1.92 mmol) was added and mixture was stirred for 30 min. Next, 1,10-phenanthroline-2,9-dicarbaldehyde (**2**; 100 mg, 0.42 mmol) was added and the resulting mixture was stirred and heated to reflux for 3 h. At the conclusion of reaction (TLC monitoring), 2 N HCl was added and reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) and the reaction mixture was stirred well and extracted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. EtOAc was removed under reduced pressure and the crude product obtained was purified by column chromatography to obtain the bis-alkene dione **3** (135 mg, 86% yield).

R_f = 0.70 (petroleum ether-EtOAc 90/10); **IR** (neat): $\tilde{\nu}_{max}$: 752, 1271, 1677, 2941, 3061, 3361, 3689, 3941 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.98-2.09 (m, 4H), 2.25-2.34 (m, 4H), 3.67 (t, J = 3.2 Hz, 4H), 4.94-5.17 (m, 4H), 5.87-5.95 (m, 2H), 7.95 (s, 2H), 8.43 (s, 4H) ppm; **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 23.76, 33.73, 37.30, 115.30, 120.87, 128.51, 131.90, 137.40, 138.45, 145.48, 153.29, 202.52 ppm; **HRMS** (Q-Tof): *m/z* calcd: 395.1729 for $C_{24}H_{24}N_2NaO_2$ [M + Na]$^+$; found 395.1730.

bis-Indole and phenanthroline derivative 5

In a typical experiment, 1.5 g of L-(+)-tartaric acid- *N*,*N′*–dimethylurea (30:70) mixture was heated to 70 °C to obtain a clear melt. To this melt, 2 mmol of *N*-methyl-*N*-phenylhydrazine and 2 mmol of bis-alkene dione **3** (40 mg, 0.11 mmol) were added at 70 °C. At the conclusion of the reaction (TLC monitoring by mini work up), the reaction mixture was quenched with water while it was still hot. The reaction mixture was cooled to rt and the solid was filtered through a sintered glass funnel and washed with water (2 × 5 mL). The crude product was dried under vacuum and then it was purified by silica gel column chromatography to obtain **5** (59 mg, 89% yield).

R_f = 0.63 (petroleum ether-EtOAc 95/5); **IR** (neat): $\tilde{\nu}_{max}$: 1067, 1244, 1634, 2926, 2958, 3028, 3675, 3928 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.44-2.50 (m, 4H), 3.08-3.12 (m, 4H), 4.07 (s, 6H), 4.90-5.05 (m, 4H), 5.83-5.94 (m, 2H), 7.13-7.17 (m, 2H), 7.25-7.32 (m, 2H), 7.42 (d, J = 8.24 Hz, 2H), 7.69 (d, J = 7.82 Hz, 2H), 7.88 (s, 2H), 7.91 (d, J = 8.30 Hz, 2H), 8.36 (d, J = 8.30 Hz, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 24.91, 31.80, 35.49, 109.92, 114.70, 116.29, 119.35, 119.81, 122.90, 125.19, 126.58, 127.51, 127.86, 136.28, 136.31, 138.44, 138.94, 146.39, 152.08 ppm; **HRMS** (Q-Tof): *m/z* calcd: 569.2681 for $C_{38}H_{34}N_4Na$ [M + Na]$^+$; found 569.2678.

General Procedure for RCM Reaction:

A solution of bis-indole-alkene derivative in dry CH_2Cl_2 (50 mL) was degassed with nitrogen for 15 min. Then, G-II catalyst (5-10 mol %) was added and reaction mixture was stirred at room temperature for 24 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc-petroleum ether) gave the RCM compound as a colourless solid.

Phenanthroline based cyclophane derivative 4

By adopting a general procedure mentioned above with substrate bis-alkene dione **3** (50 mg, 0.13 mmol) in dry CH_2Cl_2 (50 mL) was degassed with nitrogen for 15 min. Then, G-II catalyst (5 mol %) was added and reaction mixture to obtain the cyclophane derivative **4** (41 mg, 89% yield) ratio of *cis* and *trans* isomer (8:2) based on ^{1}H NMR.

R_f = 0.65 (petroleum ether-EtOAc 901); **IR** (neat): $\tilde{\nu}_{max}$: 740, 1267, 1681, 2934, 3061, 3357, 3687, 3939 cm^{-1}.; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.98-2.09 (m, 4H), 2.25-2.34 (m, 4H), 3.67 (t, *J* = 3.2 Hz, 4H), 5.60 (m, 2H), 7.95 (s, 2H), 8.43 (s, 4H) ppm. **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 23.56, 25.28, 27.97, 32.34, 40.66, 120.35, 128.32, 129.86, 130.72, 131.45, 137.07, 137.19, 145.13, 152.73, 203.01 ppm; **HRMS** (Q-Tof): *m/z* calcd: 345.1547 for $C_{22}H_{21}N_2O_2$ [M + H]$^+$; found 345.1549.

bis-Indole and phenanthroline based cyclophane derivative 6b

By adopting a general procedure mentioned above with **5** (17 mg, 0.031 mmol) in dry CH_2Cl_2 (50 mL) was degassed with nitrogen for 10 min. Then, G-II catalyst (10 mol %) was added and reaction mixture to obtain the cyclophane derivative **6b** (6 mg, 38% yield).

Mp 258-260 °C; R_f = 0.73 (petroleum ether-EtOAc 90/10); **IR** (neat): $\tilde{\nu}_{max}$: 1071, 1286, 1632, 2929, 2982, 3338, 3667, 3945 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.78-2.83 (m, 4H), 2.85-2.88 (m, 4H), 3.62 (s, 6H), 5.62 (t, *J* = 4.15 Hz, 2H), 7.13-7.16 (m, 2H), 7.25.7.28 (m, 2H), 7.33 (d, *J* = 8.20 Hz, 2H), 7.66 (d, *J* = 8.20 Hz, 2H), 7.72 (d, *J* = 7.90 Hz, 2H), 7.91 (s, 2H), 8.34 (d, *J* = 8.25 Hz, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ = 25.72, 30.27, 31.57, 109.59, 116.96, 119.34, 120.05, 122.44, 125.85, 126.97, 127.77, 127.99, 130.24, 135.92, 137.05, 138.01, 146.71, 152.55 ppm; **HRMS** (Q-Tof): *m/z* calcd: 519.2549 for $C_{36}H_{31}N_4$ [M + H]$^+$; found 519.2551.

bis-Indole and phenanthroline based cyclophane derivative 6a

Further elution of column chromatography gave the *trans* isomer **6a** (9 mg, 56% yield).

Mp 263-265 °C; R_f = 0.52 (petroleum ether-EtOAc 90/10); **IR** (neat): $\tilde{\nu}_{max}$: 1061, 1266, 1624, 2936, 2998, 3328, 3665, 3965 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.48-2.49 (m, 4H), 2.95 (t, *J* = 7.25 Hz, 4H), 3.68 (s, 6H), 5.70 (t, *J* = 3.25 Hz, 2H), 7.13-7.16 (m, 2H), 7.27-7.29 (m, 2H), 7.34 (d, *J* = 8.20 Hz, 2H), 7.66 (d, $J = 8.20$ Hz, 2H), 7.70 (d, $J = 7.90$ Hz, 2H), 7.90 (s, 2H), 8.32 (d, $J = 8.25$ Hz, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$): $\delta = 24.85$, 31.92, 32.86, 109.66, 116.72, 119.33, 120.14, 122.50, 125.52, 126.87, 127.78, 127.95, 129.80, 135.95, 137.32,138.17, 146.73, 152.64 ppm; **HRMS** (Q-Tof): *m/z* calcd: 519.2549 for $C_{36}H_{31}N_4$ $[M + H]^+$; found 519.2547.

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9. CCDC 1419802 (**6a**), CCDC 1419803 (**6b**), 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. (Hydrogen atoms are removed for better visualization.)