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# Synthesis of novel indole based cyclophanes and cylindrical cyclophanes by tandem alkylation methodology using NaH

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**Abstract**—Treatment of 1 equiv of 1,3-bis(bromomethyl)benzene and 2,6-bis(bromomethyl)pyridine with 1 equiv of indole in the presence of NaH in THF afforded the symmetrical cyclophanes **1** and **2**. Using similar methodology, cylindrical cyclophanes **3** and **4** were obtained from 2 equiv of 1,3,5-trimethyl-2,4,6-tris(bromomethyl)benzene and 1,3,5-tris(bromomethyl)benzene with 3 equiv of indole.


The synthesis of [2,2]paracyclophane[1] by Cram and Steinberg was a revolutionary breakthrough in the field of cyclophane chemistry. In the synthesis of cyclophanes, often the ring-closing step is crucial[2] and various reagents and reaction conditions have been developed for this purpose. Ueda et al. have synthesized planar, chiral paracyclophanes via samarium(II) catalyzed intramolecular pinacol coupling.[3] Novel photostable phenanthrenophanes have been synthesized by intramolecular acid catalyzed etherification from the corresponding diols.[4] Microwave methodology has also been utilized for the synthesis of cationic cyclophanes.[5] The synthesis of thiacyclophanes by a one-pot reaction, utilizing a suitable dibromide and methane dithiolate generated from double reduction of $CS_2$ with $NaBH_4$[6] has also been reported. The utility of the McMurry coupling strategy for the synthesis of stilbenophanes[7] and indolophanes[8] has also recently been explored in our laboratory.

Recently, cylindrical molecular capsules have been used for understanding isotopic effects at molecular level.[9] Cylindrical cyclophanes possessing crown ether and cyclophane subunits as building sites and a hydrophobic cavity were used for molecular recognition.[10] The syntheses of stilbene-based cylindrical indolophanes using intermolecular McMurry coupling proved unsuccessful.[8b] In addition, the synthesis of indole-based cyclophanes and cylindrical cyclophanes using NaH is still a rare observation.[11] We report herein the use of NaH for the synthesis of indolophanes **1** and **2** and cylindrical indolophanes **3** and **4** (Fig. 1).

Treatment of 1 equiv of 1,3-bis(bromomethyl)benzene **5a** with 1 equiv of indole in a slurry of NaH/THF under reflux afforded the indolophane **1**[12] in 17% yield along with the bis-N-alkylated indole **6**[13] in 25% yield. The formation of **1** was evident by the appearance of singlets at $\delta$ 4.00 and 5.10 for the *C*-methylene and *N*-methylene protons in addition to the aromatic protons in the $^1$H NMR spectrum. This confirmed the N-alkylation and C-alkylation of the *m*-xylyl unit with indole. In the $^{13}$C NMR spectrum, the *C*- and *N*-methylene carbons were observed at $\delta$ 31.0 and 49.6 along with the aromatic carbons. The structure of indolophane **1** was further confirmed by mass spectroscopy and elemental analysis. However, treatment of 1,2-bis(bromomethyl)benzene and 1,4-bis(bromomethyl)benzene with indole under similar conditions afforded only the corresponding bis-N-alkylated product. Thus, only 1,3-bis(bromomethyl)-benzene favours cyclization towards the formation of indolophane **1** along with the bis-N-alkylated product **6**. Interestingly, treatment of one equivalent of 2,6-bis(bromomethyl)pyridine **5b** with indole under the same reaction conditions afforded the indolophane **2**[14] in 15% yield along with the bis-N-alkylated indole **7**[15] in 28% yield. The $^1$H NMR spectrum of indolophane **2** exhibited *C*- and *N*-methylene protons at $\delta$ 4.57 and 5.47 in addition to the aromatic protons. Further, in the $^{13}$C NMR the *C*-methylene and *N*-methylene

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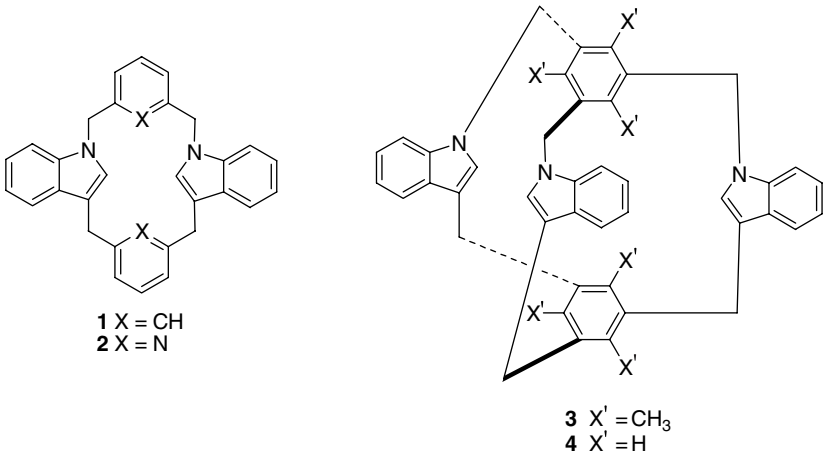


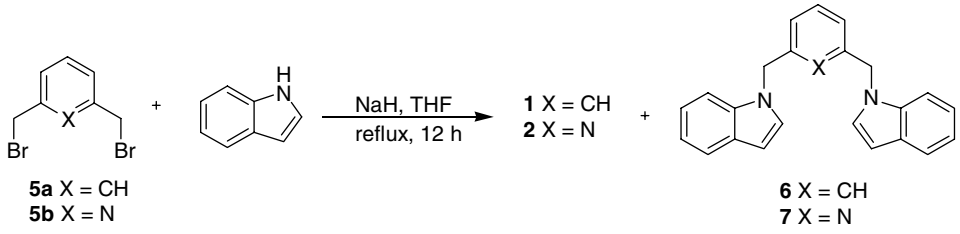

**Figure 1.** Indolophanes **1** and **2** and cylindrical indolophanes **3** and **4**.

carbons appeared at $\delta$ 33.5 and 51.7 in addition to the aromatic carbons (Scheme 1).

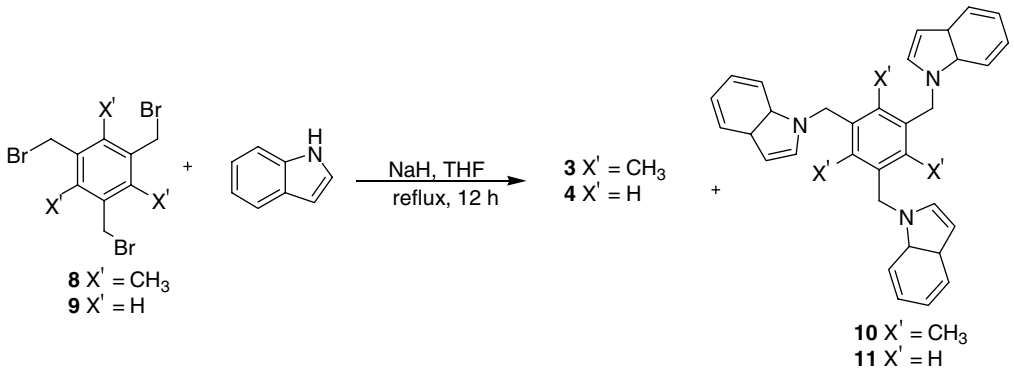
Reaction of 2 equiv of 1,3,5-trimethyl-2,4,6-tris(bromomethyl)benzene with 3 equiv of indole in NaH/THF under reflux afforded cylindrical indolophane **3**[16] in 10% yield along with tris-N-alkylated product **10**[17] in 28% yield. The $^{1}$H NMR spectrum of **3** displayed a singlet at $\delta$ 2.02 for the methyl protons attached to benzene ring. The *C*-methylene and *N*-methylene protons appeared as singlets at $\delta$ 4.04 and at $\delta$ 5.20. Two peaks for the methyl carbons at $\delta$ 15.5 and 15.6 along with the methylene carbons at $\delta$ 26.4 and 44.3 and 11 aromatic carbon peaks were observed in the $^{13}$C NMR spectrum.

The mass spectrum and elemental analysis also supported the proposed structure of the cylindrical cyclophane **3**. Using a similar reaction sequence, two equivalents of 1,3,5-tris(bromomethyl)benzene was treated with 3 equiv of indole to give cylindrical indolophane **4**[18] in 9% yield along with tris-N-alkylated product **11**[19] in 30% yield (Scheme 2). The formation of **4** was supported by $^{1}$H and $^{13}$C NMR data.

In conclusion, indolophanes[20] **1** and **2** and cylindrical indolophanes[21] **3** and **4** were synthesized by tandem C-alkylation and N-alkylation of indole using NaH. Biological and complexation studies of cyclophanes **1**–**4** are underway.




**Scheme 1.** Reagents and conditions: NaH (10 equiv), indole, THF, reflux 1 h, dibromide **5a** or **5b**, slow addition 12 h, reflux 12 h, 17% (**1**), 15% (**2**).




**Scheme 2.** Reagents and conditions: NaH (15 equiv), indole (1 equiv), THF, reflux 1 h, tribromide **8** or **9**, slow addition 12 h, reflux 12 h, 10% (**3**), 9% (**4**).

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12. Compound **1**: Yield 17%; mp 274–276 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.00 (s, 4H); 5.10 (s, 4H); 6.50 (s, 2H); 7.00 (t, 2H, $J = 7.4$ Hz); 7.07–7.10 (m, 2H); 7.14–7.15 (m, 2H); 7.20–7.24 (m, 4H); 7.27–7.36 (m, 4H); 7.47 (d, 2H, $J = 8.0$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 31.0, 49.6, 109.3, 114.9, 119.0, 119.2, 121.7, 124.6, 126.2, 126.3, 126.5, 128.7, 141.5. *m/z* (EI) 439 ($M^+$+1). Elemental Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.78; H, 5.89; N, 6.44.
13. Compound **6**: Yield 25%; mp 112–116 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.24 (s, 4H); 6.52 (d, 2H, $J = 3.4$ Hz); 6.92–6.96 (m, 4H); 7.06 (d, 2H, $J = 3.4$ Hz); 7.10–7.14 (m, 6H); 7.64 (d, 2H, $J = 8.0$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 49.9, 102.6, 109.8, 119.8, 120.8, 122.0, 125.5, 126.8, 128.3, 128.7, 129.4, 135.8, 138.3. *m/z* (EI) 336 ($M^+$). Elemental Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.74; H, 6.02; N, 8.29.
14. Compound **2**: Yield 15%; mp 250–255 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.57 (s, 4H); 5.47 (s, 4H); 6.59 (s, 2H); 7.10–7.13 (m, 2H); 7.26–7.25 (m, 2H); 7.31 (d, 4H, $J = 7.4$ Hz); 7.37 (d, 4H, $J = 7.4$ Hz); 7.50 (t, 2H, $J = 8.0$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 33.5, 51.7, 102.4, 109.7, 119.9, 120.1, 121.2, 122.1, 122.5, 123.0, 128.5, 128.9, 136.2, 138.3, 138.5. *m/z* (EI) 440 ($M^+$). Elemental Anal. Calcd for $C_{30}H_{24}N_4$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.73; H, 5.56; N, 12.67.
15. Compound **7**: Yield 28%; mp 116–120 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 5.40 (s, 4H); 6.49 (d, 2H, $J = 8.0$ Hz); 6.58 (d, 2H, $J = 2.9$ Hz); 7.10–7.13 (m, 3H); 7.15–7.18 (m, 3H); 7.26–7.28 (m, 3H); 7.66 (d, 2H, $J = 7.4$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 52.0, 102.3, 109.8, 119.5, 119.9, 121.2, 122.0, 128.5, 128.9, 136.3, 138.2, 157.5. *m/z* (EI) 337 ($M^+$). Elemental Anal. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.85; H, 5.71; N, 12.43.
16. Compound **3**: Yield 10%; mp 298–302 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.02 (s, 18H); 4.04 (s, 6H); 5.20 (s, 6H); 5.25 (s, 3H); 7.20–7.23 (m, 3H); 7.31 (t, 3H, $J = 7.6$ Hz); 7.47 (d, 3H, $J = 7.6$ Hz); 7.74 (d, 3H, $J = 7.6$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 15.5, 15.6, 26.4, 44.3, 109.2, 114.3, 119.3, 121.6, 123.1, 128.7, 131.3, 133.6, 135.5, 137.2, 139.8. *m/z* (EI) 663 ($M^+$). Elemental Anal. Calcd for $C_{48}H_{45}N_3$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.76; H, 6.86; N, 6.37.
17. Compound **10**: Yield 28%; mp 130–132 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.14 (s, 9H); 4.68 (s, 6H); 6.53 (d, 3H, $J = 8.0$ Hz); 6.79 (m, 3H); 7.06–7.12 (m, 6H); 7.19–7.25 (m, 3H); 7.45 (d, 3H, $J = 7.6$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 14.1, 48.3, 100.2, 109.4, 117.6, 121.2, 123.7, 124.5, 126.4, 132.3, 134.1. *m/z* (EI) 507 ($M^+$). Elemental Anal. Calcd for $C_{33}H_{27}N_3$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.14; H, 6.51; N, 8.32.
18. Compound **4**: Yield 9%; mp 286–290 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.90 (s, 6H); 5.06 (s, 6H); 5.24 (s, 3H); 7.00 (s, 3H); 7.17 (m, 3H); 7.25 (m, 3H); 7.32–7.34 (m, 3H); 7.43 (d, 3H, $J = 7.6$ Hz); 7.67 (d, 3H, $J = 7.6$ Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 29.3, 46.4, 110.4, 115.1, 118.2, 121.6, 123.2, 125.4, 128.9, 137.4, 138.2, 139.4, 142.3. *m/z* (EI) 579 ($M^+$). Elemental Anal. Calcd for $C_{42}H_{33}N_3$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.05; H, 5.78; N, 7.22.
19. Compound **11**: Yield 30%; mp 124–126 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 4.77 (s, 6H); 6.54 (s, 3H); 6.97–7.01 (m, 6H); 7.18–7.23 (m, 6H); 7.38 (d, 3H, $J = 8.0$ Hz); 7.64 (d, 3H, $J = 7.4$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 49.8, 102.6, 110.0, 119.8, 120.7, 121.9, 122.4, 124.1, 127.8, 135.7, 136.0. *m/z* (EI) 465 ($M^+$). Elemental Anal. Calcd for $C_{33}H_{27}N_3$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.16; H, 5.82; N, 9.08.
20. Typical procedure for the synthesis of indolophanes **1** and **2**: To a slurry of 42 mmol of NaH in 20 mL of dry THF in a three-necked round bottom flask under an $N_2$ atmosphere, 4 mmol of indole dissolved in 30 mL of dry THF was added dropwise and the mixture refluxed for 1 h. Dibromide (5 mmol) was dissolved in 200 mL of THF and added to the above reaction mixture with stirring for 12 h and then at reflux for a further 12 h. The reaction mixture was quenched with aq $NH_4Cl$ solution to remove excess NaH and THF was removed under reduced pressure. The

residue was extracted with $CHCl_3$ and dried over anhydrous $Na_2SO_4$. The crude product was purified by column chromatography on silica gel, using $CHCl_3$–hexane (1:3) as eluent to give indolophanes **1** and **2** as light sensitive white solids.

21. An identical procedure was adopted for the syntheses of cylindrical cyclophanes **3** and **4**, which were obtained as light sensitive white solids. Reagents: NaH (16.5 mmol) in 20 mL THF; indole (1.1 mmol) in 30 mL THF and tribromide (1.2 mmol) in 200 mL THF.