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Tandem one-pot intra- and inter-molecular McMurry coupling for the synthesis of bisindolostilbenophanes

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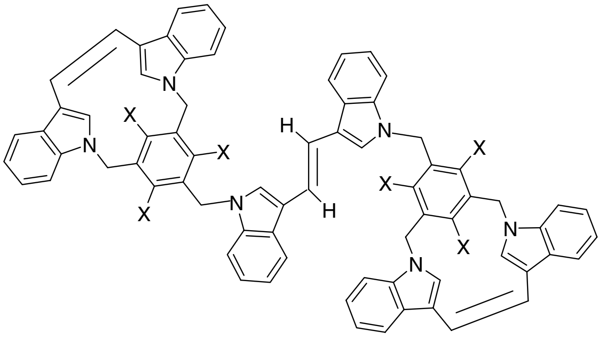
Abstract—Treatment of 3 equiv of indole-3-aldehyde with 1,3,5-trimethyl-2,4,6-tris(bromomethyl)benzene and 1,3,5-tris(bromomethyl)benzene gave the tris-alkylated products, which underwent both intra- and inter-molecular McMurry coupling in one-pot with low valent titanium to give indole-based stilbenophanes.

Recently, the use of the McMurry coupling reaction in the field of organic[1] and supramolecular chemistry[2] has been used extensively to synthesize fascinating molecules. Intramolecular McMurry coupling reactions have become an important tool to make symmetrical and unsymmetrical hydroxystilbenes[3] and highly distorted cone calix[4]arenes[4] and porphyrin derivatives from tetrapyrroledialdehyde.[5] The intramolecular McMurry coupling was also a key step in encapsulation of molecular hydrogen in fullerene C_{60}.[6] Artificial molecular devices like light-driven molecular motors[7] were developed using intramolecular McMurry couplings. Although bicyclic and bis-cyclic cyclophanes[8] have been synthesized using high dilution techniques in our laboratory, Lee et al. have synthesized bicyclic and bis-cyclic orthocyclophanes[9] through intramolecular McMurry coupling. The potential of inter- and intra-molecular McMurry coupling in the synthesis of stilbenophanes[10] and indolophanes[11] was reported from our laboratory recently. However, to the best of our knowledge, there is no report of a similar molecule undergoing a one-pot, tandem intra- and inter-molecular McMurry coupling. Hence, we were interested in studying the application of tandem intra- and inter-molecular McMurry coupling for the synthesis of indole based stilbenophanes **1a** and **1b** from the corresponding trialdehydes.



1a X = CH_3
1b X= H

The tribromide **3a** was prepared by bromomethylation of mesitylene.[12] N-alkylation of the tribromide **3a** with 3 equiv of indole-3-aldehyde **4**, afforded precyclophane **5a** in an 80% yield.

The formation of precyclophane **5a** was evident from the presence of three singlets at δ 2.28 for methyl, δ 5.43 for NCH_2 and δ 9.89 for the aldehydic protons, respectively, in addition to aromatic protons in the ^1H NMR spectra. The structure was further confirmed by ^{13}C NMR spectroscopy by the appearance of a methyl carbon at δ 16.6, a methylene carbon at δ 45.5 and an aldehydic carbon at δ 184.6 in addition to the aromatic carbons. Preindolophane **5a** can undergo intermolecular McMurry coupling to give the cylindrophane **2a**,[13a,b] which is also a rare class of cyclophanes, but interestingly, the precyclophane **5a** underwent both intra- and

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Keywords: Biscyclophanes; Indolostilbenophanes; One-pot intra- and inter-McMurry coupling.

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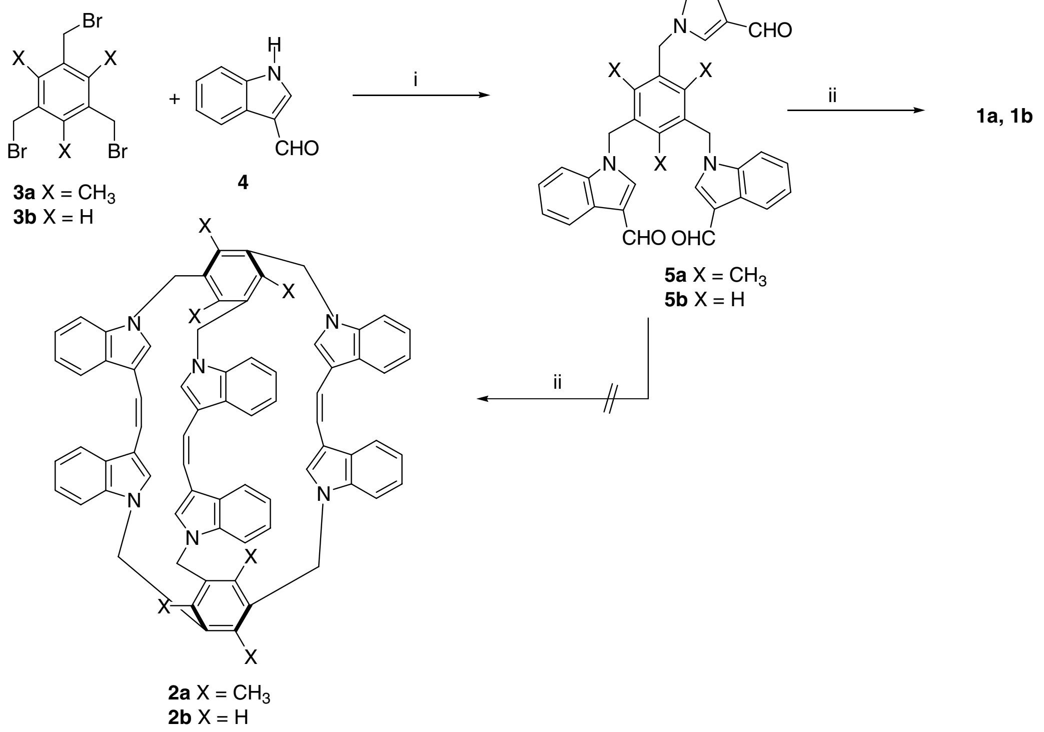
inter-molecular coupling simultaneously on treatment with $TiCl_4$ and Zn in THF under refluxing conditions to give the bisindolophane based stilbenophane **1a** in 24% yield. If all the three aldehydic groups coupled



Scheme 1. Reagents and conditions: (i) CH_3CN, 25% NaOH, rt, 48 h, 80% (**5a**), 78% (**5b**); (ii) $TiCl_4$ (20 equiv), Zn (40 equiv), THF, py, reflux, 12 h, 24% (**1a**), 22% (**1b**).

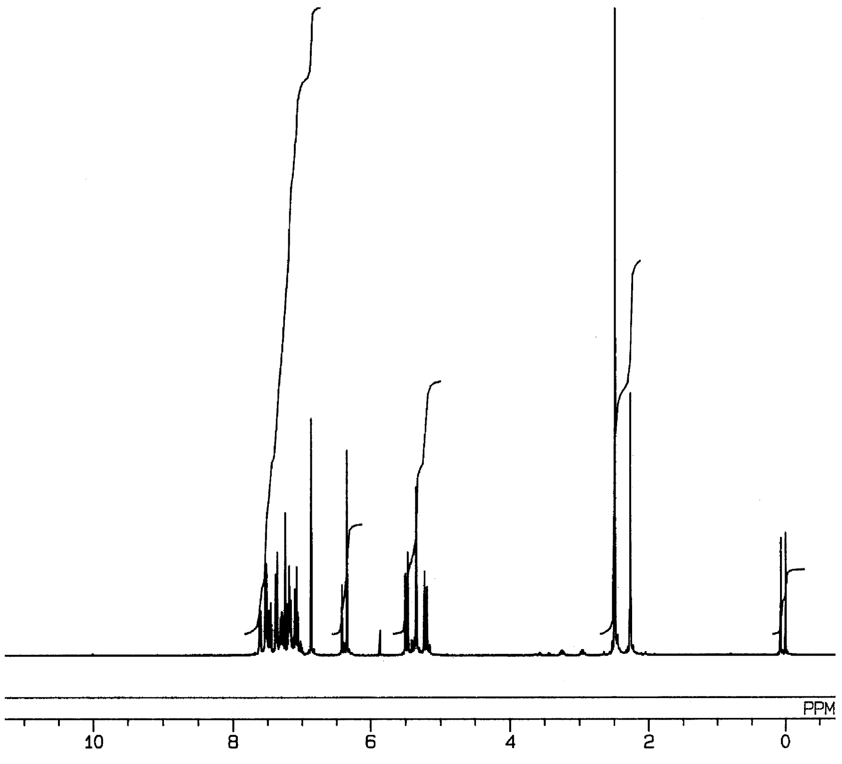


Figure 1. The ^{1}H NMR spectrum of compound **1a**.

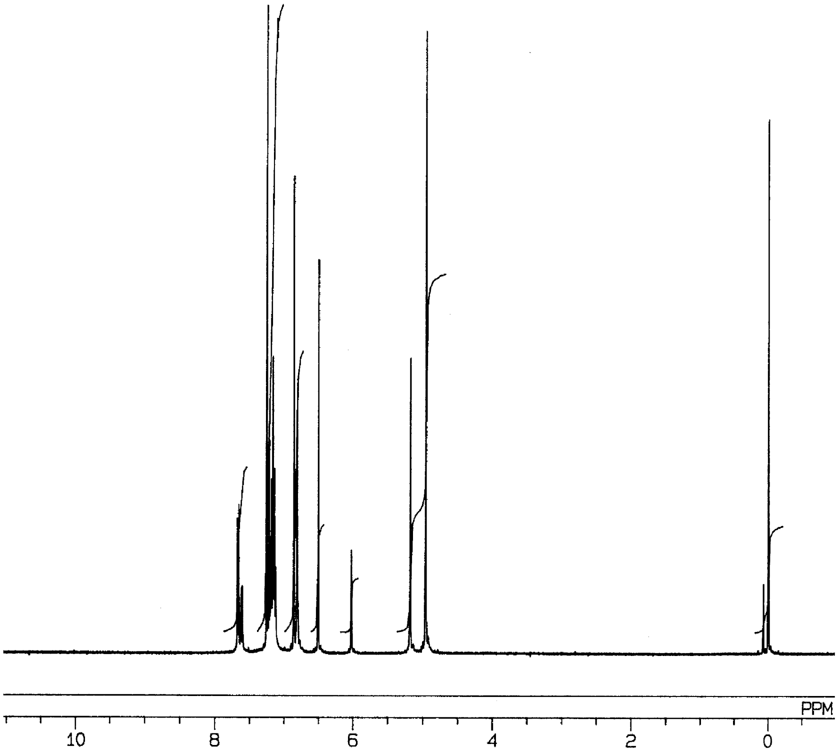


Figure 2. The ^{1}H NMR spectrum of compound **1b**.

intermolecularly, the methyl, methylene and olefinic protons in the cyclophane have to appear as singlets. Instead, two sets of peaks were observed for the methyl, methylene and olefinic protons in the ^{1}H NMR[14] and the integration of one peak is double that of the other. In indolostilbenophane **1a** amongst the six methyl groups of the mesityl units, six protons belonging to two methyl groups present inside the cavity were shielded and appeared at δ 2.26 and the remaining 12 protons belonging to the other four methyl groups present outside the cavity were deshielded and appeared at δ 2.48. This pattern was also present for the methylene and vinylic protons. Among the six methylene groups present in **1a**, protons belonging to four methylene groups, which are part of the rings appeared as two doublets ($J = 14.3$ Hz) and the remaining two methylene protons appeared as a singlet (Fig. 1). In the case of the vinylic protons, four appeared as a singlet at δ 6.35 and the remaining two protons appeared as another singlet at δ 6.42. The structure of the cyclophane **1a** was also confirmed by FAB mass and elemental analysis.

To confirm that the non-equivalence of the methylene protons was due to hindered rotation, tribromide **3b**[15] was reacted with indole-3-aldehyde to give precyclophane **5b** in a 78% yield. The formation of **5b** was confirmed by the presence of the NCH_2 protons as a singlet at δ 5.22 and the appearance of the aldehydic protons at δ 9.90 in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum the methylene carbons appeared at δ 50.4 and the aldehydic carbons at δ 184.6. The trialdehyde on treatment with low valent titanium under the above mentioned conditions afforded cyclophane **1b** in 22% yield (Scheme 1).

The ^{1}H NMR spectrum of **1b**[16] displayed two singlets at δ 4.95 and 5.17 representing two different types of methylene protons. Therefore, the methylene protons, which are part of the ring, also appeared as a singlet and not as a pair of doublets (Fig. 2). The remaining olefinic and aromatic protons appeared as two sets of peaks. In the ^{13}C NMR spectrum two different methylene carbons appeared as two peaks at δ 49.0 and δ 49.5 and 20 peaks were observed in the aromatic region. The structure of cyclophane **1b** was also confirmed further by FAB mass and elemental analysis.

In conclusion, the indolostilbenophanes **1a** and **1b** were obtained from the corresponding trialdehyde by a one-pot tandem intra- and inter-molecular McMurry coupling. Synthesis of other such indolostilbenophanes and studies of their complexation with electron deficient molecules as well as their biological activities are underway.

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14. Compound **1a**: Yield 24%; mp 222–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 6H); 2.48 (s, 12H); 5.23 (d, 4H, $J = 14.3$ Hz); 5.35 (s, 4H); 5.50 (d, 4H, $J = 14.3$ Hz); 6.35 (s, 4H); 6.42 (s, 2H); 6.87 (s, 4H); 7.08 (t, 4H, $J = 7.45$ Hz); 7.17–7.20 (m, 6H); 7.25 (s, 2H); 7.29 (t, 2H, $J = 8$ Hz); 7.38 (d, 4H, $J = 8.05$ Hz); 7.47 (d, 2H, $J = 8$ Hz); 7.53 (d, 4H, $J = 8.0$ Hz); 7.62 (d, 2H, $J = 7.45$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.2, 16.7, 44.6, 44.7, 108.9, 109.0, 110.8, 111.9, 119.1, 119.3, 119.7, 119.8, 121.7, 123.0, 127.4, 127.5, 128.0, 129.2, 130.8, 135.1, 136.7, 137.2, 137.4, 141.2; m/z (FAB-MS) 1087 (M^+). Elemental anal. Calcd for $C_{78}H_{66}N_6$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.11; H, 6.05; N, 7.68.
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16. Compound **1b**: Yield 24%; mp 282–289 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (s, 8H); 5.17 (s, 4H); 6.01 (s, 2H); 6.50 (s, 4H); 6.81 (s, 4H); 6.85 (s, 6H); 7.11–7.25 (m, 20H), 7.61 (d, 2H, $J = 7.45$ Hz), 7.67 (d, 4H, $J = 7.45$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 49.0, 49.5, 109.5, 109.8, 111.2, 113.8, 119.0, 119.2, 119.4, 119.8, 121.9, 124.2, 124.7, 125.1, 125.2, 128.1, 128.2, 129.0, 129.5, 136.7, 137.5, 137.8, 139.3; m/z (FAB-MS) 1002 (M^+). Elemental anal. Calcd for $C_{72}H_{54}N_6$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.12; H, 5.37; N, 8.34.