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The use of McMurry coupling for the synthesis of indolophanes and *cis*-stilbenophanes

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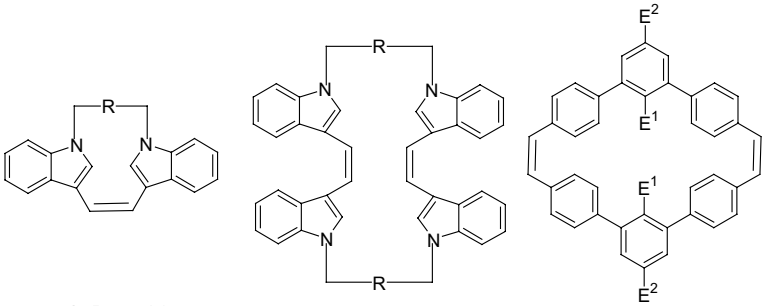
Abstract—Treatment of 2 equiv of indole-3-aldehyde with *o*, *m*, *p*-xylyl, 2,5-dimethoxy-*p*-xylyl dibromides and 4,4′-bis(bromomethyl)-1,1′-biphenyl gave the bisalkylated products, which underwent McMurry coupling with low valent titanium to give indolophanes. Various *cis*-stilbenophanes with *m*-terphenyl building blocks were also synthesized by application of the McMurry coupling technique.

Low valent titanium has been extensively used in organic synthesis[1] and its use for the synthesis of cyclophanes has gained momentum during recent times.[2,3] The synthesis of cyclic paraphenylacetylenes and paraphenylethylenes through McMurry coupling has been reported recently.[4] The application of intermolecular[5] and intramolecular[6] McMurry coupling for the synthesis of potentially useful stilbenophanes is known. In addition McMurry coupling has been used for the synthesis of molecular clocks[7] and [12]annulenes[8] and has attracted the attention of synthetic chemists. Coupling using low valent titanium for the synthesis of ferrocenophanes[9] and in the synthesis of (6,6)-metacyclophanes with enediyne bridges[10] has proved the utility of McMurry coupling in supramolecular chemistry. The indole moiety is present in a number of natural products[11] and is known to be a bioactive nucleus.[12] Indole based cyclophanes[13] are of interest because they are infrequently encountered[14] systems. The synthesis of indole based cyclophanes[15,16] have recently been reported; they have the ability to form complexes with metals such as cobalt.[17] Hence, we are interested in studying the application of the McMurry coupling for the synthesis of indolophanes **1a**–**e**, **2a**–**e** and stilbenophanes **3a**–**d**.



1a R= *o*-xylyl
1b R= *m*-xylyl
1c R= *p*-xylyl
1d R= 2,5-dimethoxy-*p*-xylyl
1e R= 4,4'-bis(methylene) -1,1'-biphenyl

2a R= *o*-xylyl
2b R= *m*-xylyl
2c R= *p*-xylyl
2d R= 2,5-dimethoxy-*p*-xylyl
2e R= 4,4'-bis(methylene) -1,1'-biphenyl

3a E^1= H, E^2=H
3b E^1=Br, E^2=H
3c E^1=CO_2Me, E^2=H
3d E^1=H, E^2=Br

Keywords: Indolophanes; Stilbenophanes; McMurry coupling.
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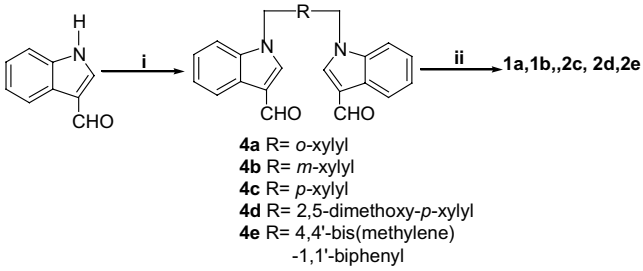
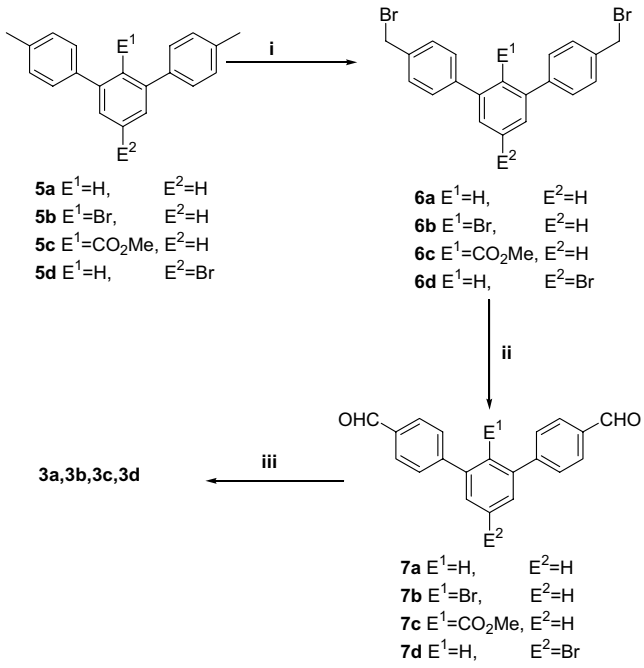
Indole-3-aldehyde[18] prepared by the formylation of indole with $POCl_3$ in DMF reacts with *o*-xylenyl dibromide in CH_3CN for 2 days in the presence of NaOH to give the precyclophane **4a**. The formation of precyclophane **4a** was evident from the presence of NCH_2 protons as a singlet at δ 5.3 in the ^1H NMR spectrum. When 1 equiv of the precyclophane **4a** was treated with 20 equiv of $TiCl_4$ and 40 equiv of Zn in THF under reflux, indolophane **1a** was obtained in 19% yield.[19] When the precyclophane **4a** was added slowly to a mixture of $TiCl_4$ and Zn, the yield of the indolophane **1a** was poor. Hence the precyclophane was added in one portion to the stirred solution of $TiCl_4$ and Zn in THF and then the mixture refluxed overnight. The use of other solvents such as dioxane, DMF and toluene gave either a mixture of inseparable products or led to the recovery of unreacted precyclophane. The ^1H NMR spectrum of indolophane **1a** displayed benzylic protons as a singlet at δ 5.8 and the olefinic protons at δ 6.72 along with the aromatic protons. The ^{13}C NMR spectrum of indolophane **1a** showed an NCH_2 carbon at δ 46.21 in addition to aromatic carbons. The formation of **2a** was not observed under the various conditions investigated due to steric hindrance resulting from the *o*-xylenyl spacer unit. Similarly the precyclophane **4b** derived from indole-3-aldehyde and *m*-xylyl dibromide formed indolophane **1b**[20] in 24% yield.

However, when a similar sequence was applied to the precyclophane **4e** derived from indole-3-aldehyde and *p*-xylyl dibromide, the dimeric product **2c**[21] was obtained in 20% yield. Similarly indolophanes **2d**[22] and **2e**[23] were obtained from the precyclophanes **4d** and **4e** in 23% and 18% yields, respectively (Scheme 1) and were fully characterized from spectral and analytical data.

Cyclophanes of the type **3a**–**d** have been reported earlier, via a multi-step route, by Hart and Rajakumar[24] However, the earlier method could not be used for the synthesis of intraannularly functionalized cyclophanes and the yields were relatively low and also involved a number of steps. However, in the current investigation, the dialdehydes **7a**–**d** were prepared as shown in Scheme 2 and McMurry coupling of 1 equiv of the dialdehydes **7a**–**d** with 20 equiv of $TiCl_4$ and 40 equiv of Zn in THF afforded the stilbenophanes **3a**,[25] **3b**,[26] **3c**[27] and **3d**[28] in 24%, 18%, 25% and 24% yields. The *m*-terphenyl systems required for the synthesis were obtained by the application of Hart's reaction.[29]



Scheme 1. Reagents and conditions: (i) *o*, *m*, *p*-2,5-dimethoxy-*p*-xylyl dibromide, 4,4′-bis(bromomethyl)-1,1′-biphenyl, CH_3CN, 25% NaOH, 48 h; (ii) $TiCl_4$ (20 equiv), Zn (40 equiv), THF, py, reflux overnight.



Scheme 2. Reagents and conditions: (i) NBS (2.1 equiv), benzoyl peroxide, CCl_4, reflux, 40 h; (ii) TBADC, $CHCl_3$, reflux, 6 h; (iii) $TiCl_4$ (20 equiv), Zn (40 equiv), pyridine, THF, reflux, 6 h.

In conclusion, the McMurry coupling has been applied for the synthesis of indolophanes and the same technique has also been utilized for the synthesis of various stilbenophanes via a shorter route and in better yields than the earlier reported procedure.[24] Complexation studies of the indolophanes and stilbenophanes are underway.

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19. **1a**: Yield 19%; mp 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.8 (s, 4H); 6.3 (s, 2H); 6.72 (s, 2H); 7.29 (t, 2H, $J = 7.45$ Hz); 7.46 (d, 4H, $J = 8.6$ Hz); 7.64 (t, 2H, $J = 7.45$ Hz); 7.79 (d, 2H, $J = 8.6$ Hz); 8.17 (d, 2H, $J = 7.4$ Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$): δ 46.21, 108.45, 112.02, 119.37, 120.04, 124.17, 125.12, 128.91, 129.53, 130.28, 136.41, 153.91, m/z (FAB-MS) 360 (M^+).
20. **1b**: Yield 24%; mp 297 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (s, 4H); 6.09 (s, 1H); 6.49 (s, 2H); 6.79 (s, 2H); 7.06–7.12 (dd, 4H, $J = 7.8$ Hz); 7.14–7.18 (m, 3H); 7.23 (d, 2H, $J = 7.8$ Hz); 7.59 (d, 2H, $J = 7.3$ Hz); ^{13}C NMR (100.4 MHz, $CDCl_3$) 49.63, 110.06, 114.21, 119.65, 120.13, 122.18, 124.96, 126.05, 126.18, 128.06, 128.50, 138.03, 139.03, m/z (FAB-MS) 360 (M^+).
21. **2c**: Yield 20%; mp 135 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 5.13 (s, 8H); 6.77 (s, 4H); 6.94 (s, 4H); 7.05 (dd, 8H, $J = 7.84$, 7.8 Hz); 7.14 (d, 8H, $J = 8.28$ Hz); 7.50 (d, 8H, $J = 7.8$ Hz); m/z (FAB-MS) 720 (M^+).
22. **2d**: Yield 23%; mp 134 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 3.49 (s, 12H); 5.11 (s, 8H); 6.24 (s, 4H); 6.80 (s, 4H); 7.02 (t, 4H, $J = 7.32$ Hz); 7.09 (m, 8H); 7.21 (d, 4H, $J = 8.32$ Hz); 7.48 (d, 4H, $J = 7.8$ Hz); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 44.47, 55.87, 55.91, 109.49, 110.62, 111.10, 118.60, 118.90, 121.45, 125.95, 126.02, 128.80, 136.77, 150.80, m/z (FAB-MS) 840 (M^+).
23. **2e**: Yield 18%; mp 137 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 5.2 (s, 8H); 6.84 (s, 4H); 7.07–7.18 (m, 20H); 7.38 (d, 8H, $J = 8.28$ Hz); 7.52 (d, 8H, $J = 7.3$ Hz); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 49.51, 109.42, 110.54, 118.83, 119.06, 121.65, 125.77, 127.25, 127.33, 128.98, 136.68, 137.03, m/z (FAB-MS) 872 (M^+).
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25. **3a**: Yield 24%; mp >300 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 6.74 (s, 4H); 7.06 (d, 8H, $J = 8.3$ Hz); 7.36 (d, 8H, $J = 8.2$), 7.42–7.50 (m, 8H); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 124.90, 124.98, 126.91, 129.20, 129.83, 130.96, 136.58, 140.19, 141.62; m/z (FAB-MS) 508 (M^+).
26. **3b**: Yield 18%; mp >300 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 6.78 (s, 4H); 6.91(d, 8H, $J = 8.32$ Hz); 7.25 (d, 8H, $J = 8.32$ Hz); 7.32–7.42 (m, 6H); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 125.21, 124.69, 127.12, 128.12, 128.94, 130.66, 135.46, 139.64, 142.67; m/z (FAB-MS) 666 (M^+).
27. **3c**: Yield 25%; mp >300 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 3.37 (s, 6H); 6.86 (s, 4H); 7.22 (d, 8H, $J = 7.8$ Hz); 7.36 (d, 8H, $J = 7.84$ Hz) 7.41–7.48 (m, 6H); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 51.49, 125.75, 126.4, 127.04, 127.19, 129.42, 130.4, 138.12, 139.68, 140.54, 205.47; m/z (FAB-MS) 624 (M^+).
28. **3d**: Yield 24%; mp >300 °C; ^{1}H NMR (400 Hz, $CDCl_3$): δ 6.74 (s, 4H); 7.04 (d, 8H, $J = 7.8$ Hz); 7.31 (d, 8H, $J = 8.31$ Hz); 7.42–7.64 (m, 6H); ^{13}C NMR (100.4 Hz, $CDCl_3$): δ 123.32, 123.61, 126.02, 126.6, 126.96, 128.66, 133.37, 139.03, 143.92; m/z (FAB-MS) 666 (M^+).
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