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Meta-terphenyls as Building Blocks for Pyridinophanes

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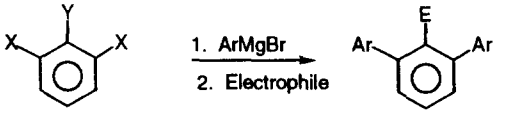
Abstract: Pyridinophanes **6** and **7** were prepared in good yield from bis(thiomethyl)-*m*-terphenyls **2** and **12** and bis (chloromethyl) pyridine derivative **11**.

Pyridinophanes have been synthesized by a variety of methods[1] and used as model systems to study diastereo- and enantioselectivity in certain biochemically important reactions, for example hydride transfer and asymmetric carbonyl reduction in NADH models, or transaminase and aldolase selectivity in pyridoxal models.[2] We describe here a short route to new pyridinophanes that incorporate a *m*-terphenyl moiety which may contain intra-annularly directed functionality (in addition to the pyridine nitrogen).

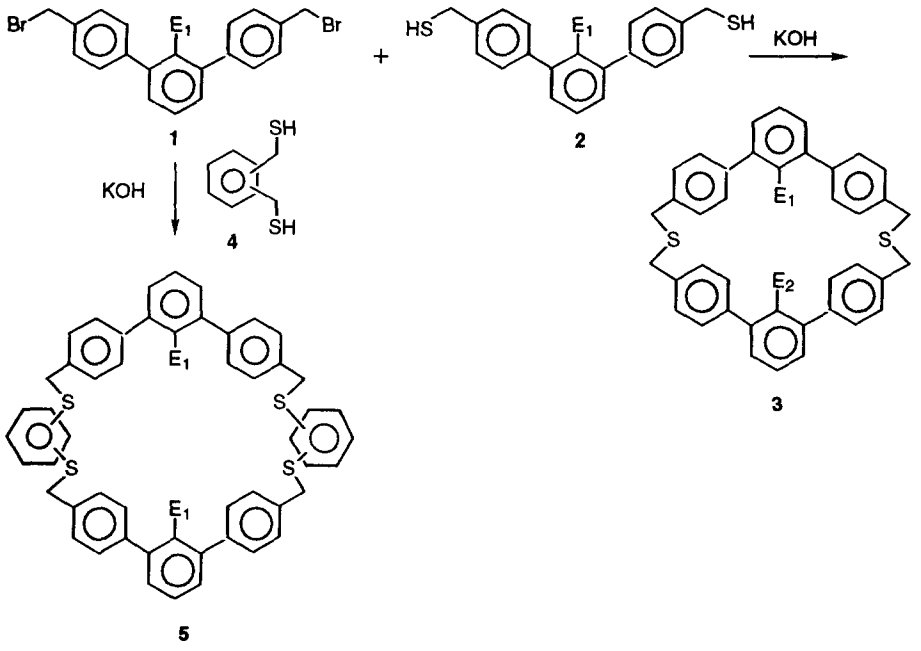
m-Terphenyls with a substituent E at the 2'-position are readily prepared in one operation by the reaction of aryl Grignard reagents with 1,2,3-trihalobenzenes.[3] The mechanism involves metal-halogen exchange at Y followed by two successive elimination-nucleophilic additions via aryne intermediates. Electrophilic quenching then places a substituent E at the 2' -position of the resulting *m*-terphenyl (eq 1).



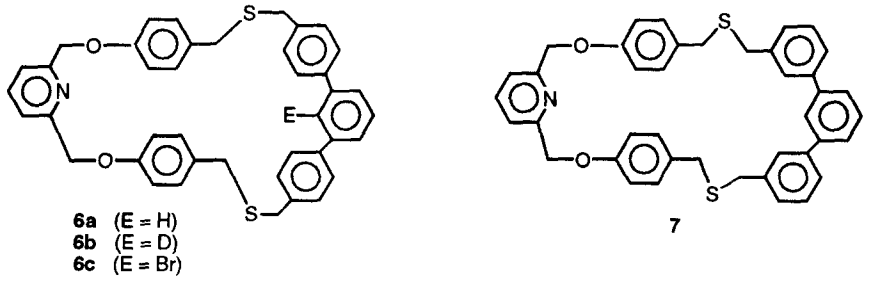
(1)

X = Cl, Br; Y = Br, I

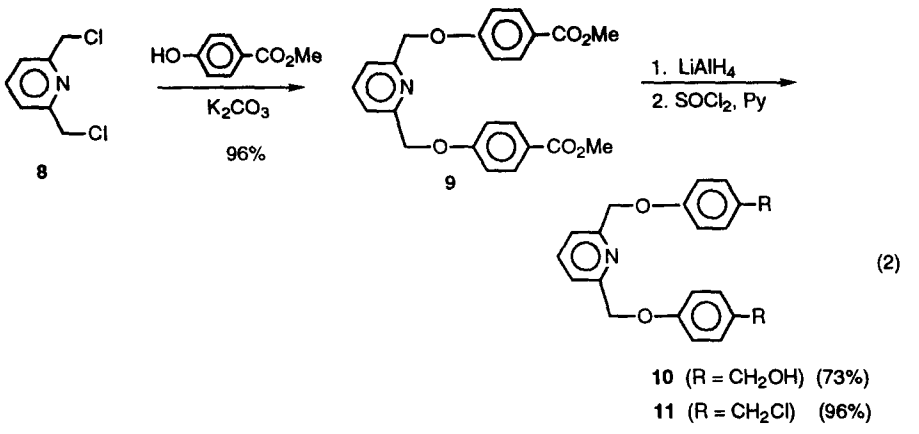
We recently described how such terphenyls can be used to rapidly assemble cyclophanes with intra-annular functionality.[4] For example, the easily prepared bis-bromide **1** and bis-thiol **2** can be coupled with base to give cyclophane **3**; alternatively, **1** can be coupled with other bis-thiols such as the *o*-, *m*- or *p*- xylylenedithiols **4** to give **5**. Examples of E_1 and E_2 in this Scheme include D, Br, I, CO_2H, CN, COCl and CO_2CH_3. Yields are good and the methodology is short.



As an extension of this technology to the synthesis of heterocyclophanes, we describe here the synthesis of pyridinophanes **6** and **7**.

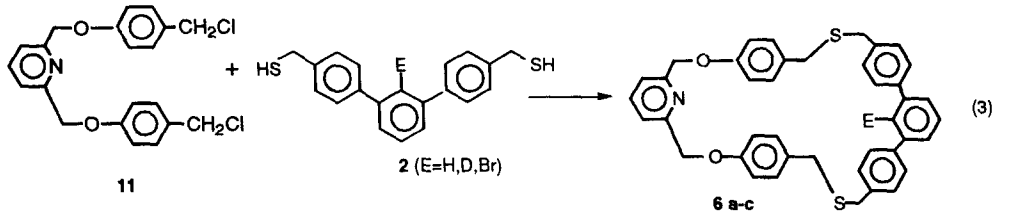


Coupling of dichloride **11**, prepared as shown (eq. 2) in three steps and 67% overall yield from 2,6-bis(chloromethyl) pyridine **8**,[5] with bis-thiols **2** and KOH in ethanol gave cyclophanes **6a** and **6b**



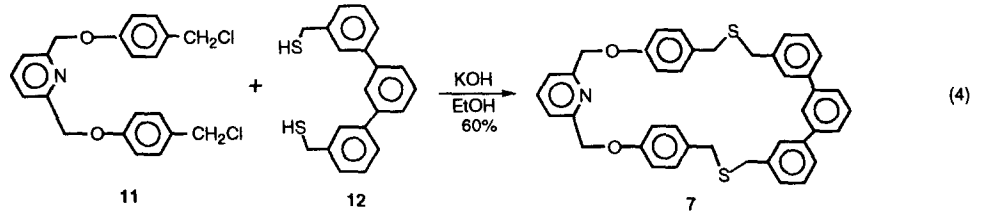
(2)

in 80% and **6c** in 40% yields (eq. 3).



(3)

In a similar manner, **11** was coupled with dithiol **12**[4] to give **7** in 60% yield (eq. 4).



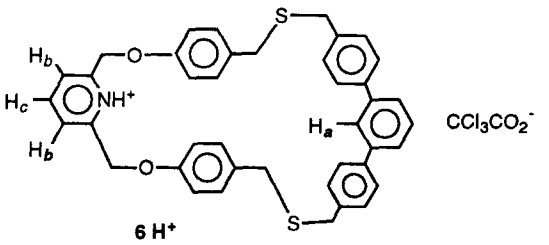
(4)

The structures of **6** and **7** were clear from their various spectra. The ^{1}H NMR spectrum of **6a** showed the expected singlets at δ 3.37 and 3.54 (4 H each) for the methylenes adjacent to sulfur and at δ 5.15 (4 H) for the methylenes adjacent to the pyridine ring. Curiously, in **6c** the latter appeared as two singlets at δ 5.02 and 5.06 which, however, sharpened to one 4-proton singlet at 105 °C in toluene-d_6; this may be due to some restrictions in conformational rotations as a consequence of the large bromine substituent. The internal aromatic proton (at E) in **6a** appeared at lowest field (δ 7.63, t, J = 1.8 Hz,

meta coupling), consistent with the chemical shift of the internal proton in analogous cyclophanes **3**[4]; this assignment was verified by the absence of this peak in **6b**.

In **7**, the aromatic proton at lowest field (δ 7.66, t, J = 8.16 Hz, ortho coupling) could be assigned to the proton para to the pyridine nitrogen. Other spectral data (^{13}C NMR, mass) verify the assigned structures.

A solution of **6a** and one equivalent of trichloroacetic acid in $CDCl_3$, left overnight, apparently formed the ion **6H$^+$**; Ha still appeared as a triplet at δ 7.64 (J = 1.7 Hz), unaffected by the proton on



6 H$^+$

nitrogen, but now the protons on the pyridine ring appeared at lower field (H_b at δ 7.66, d, J = 8.1 Hz, 2 H and H_C at δ 8.08, t, J = 8.1 Hz, 1 H) and the proton on nitrogen could be observed as a broad singlet at δ 13.2. Since the other aryl protons and the methylene protons were only slightly affected, the trichloroacetate anion is probably not "inside" the cyclophane ring.

In this short paper, we described the synthesis of cyclophane building block **11** and pyridinophanes **6** and **7**. Extension to other heterophanes based on the *m*-terphenyl framework along similar lines is undoubtedly possible.[6]

Experimental Section[7]

2,6-Bis(4-carbomethoxyphenoxy) lutidine (9). A mixture of methyl *p*-hydroxybenzoate (14.6 g, 96.1 mmol), 2,6-bis (chloromethyl) pyridine[5] (8.0 g, 45.8 mmol) and 15 g of anhydrous K_2CO_3 in 100 mL of anhydrous DMF was stirred under Ar at room temperature for 48 h, then poured with vigorous stirring into water (300 mL). The resulting white precipitate was filtered, washed with water (3X) and dissolved in CH_2Cl_2 (350 mL). This solution was washed with 5% aqueous NaOH (3X), dried ($MgSO_4$) and evaporated to yield 17.8 g (96%) of **9** as a white solid, mp 175 °C: ^1H NMR δ 3.84

(s, 6 H), 5.22 (s, 4 H), 6.97 (d, J = 8.8 Hz, 4 H), 7.41 (d, J = 7.7 Hz, 2 H), 7.72 (t, J = 7.7 Hz, 1 H), 7.96 (d, J = 8.8 Hz, 4 H); mass spectrum, *m/e* (relative intensity) 407 (23), 376 (11), 256 (100). Anal. Calcd for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.20. Found: C, 67.63; H, 5.48.

2,6-Bis(4-hydroxymethylphenoxy) lutidine (10). To a solution of diester **9** (17.5 g, 43.0 mmol) in 500 mL of anhydrous THF was added in portions 2.45 g (64.5 mmol) of $LiAlH_4$ at room temperature. The resulting solution was heated at reflux for 6 h, cooled, and quenched by adding successively water (2.5 mL), 15% NaOH (2.5 mL) and water (5 mL). The inorganic precipitate was removed by filtration and the filtrate was evaporated to yield a white solid which was recrystallized from a minimum of THF: MeOH (3:1) to yield 11.0 g (73%) of **10** as a white solid, mp 153 °C: ^{1}H NMR (DMSO-d_6) δ 4.39 (d, J = 5.4 Hz, 4 H), 5.06 (t, J = 5.4 Hz, 2 H), 5.16 (s, 4 H), 6.96 (d, J = 8.4 Hz, 4 H), 7.20 (d, J = 8.4 Hz, 4 H), 7.43 (d, J = 7.8 Hz, 2 H), 7.84 (t, J = 7.8 Hz, 1 H); mass spectrum, *m/e* (relative intensity) 351 (12), 333 (100), 228 (80), 222 (91). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02. Found: C, 71.28; H, 6.08.

2,6-Bis(4-chloromethylphenoxy) lutidine (11). To a suspension of diol **10** (8.5 g, 24.2 mmol) in $CHCl_3$ (300 mL) was added over 1 h a solution of $SOCl_2$ (5.91 g, 50.2 mmol) in 35 mL of $CHCl_3$, and the mixture was stirred at room temperature for an additional 10 h. The mixture was washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated to give 9.0 g (96%) of **11** as a white solid, mp 118-120 °C (benzene); ^{1}H NMR δ 4.57 (s, 4 H), 5.23 (s, 4 H), 6.98 (d, J = 8.6 Hz, 4 H), 7.33 (d, J = 8.6 Hz, 4 H), 7.46 (d, J = 7.7 Hz, 2 H), 7.76 (t, J = 7.7 Hz, 1 H); ^{13}C NMR δ 46.1, 70.1 115.0, 120.5, 130.1 138.2, 156.3, 158.3; mass spectrum, *m/e* (relative intensity) 389 (21), 388 (9), 387 (33), 352 (76), 246 (100), 140 (81). Anal. Calcd for $C_{21}H_{19}Cl_2NO_2$: C, 64.96; H, 4.93. Found: C, 65.01; H, 5.01.

General Procedure for Coupling 11 with Bisthiols. A solution of dichloride **11** (2.0 mmol) and the bisthiol (2.0 mmol) in 500 mL of Ar-degassed benzene was added dropwise over 24 h to a solution of KOH (4.0 mmol) in 800 mL of 95% ethanol under Ar. After further stirring for 4-5 h, the mixture was evaporated to dryness and the residue was extracted with CH_2Cl_2 (2 x 150 mL) and the extract was washed with water (2 x 100 mL), dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel, $CHCl_3$) and recrystallized from hexane: CH_2Cl_2 (1:1 v/v) to yield the pure cyclophane.

Cyclophanes 6a and 6b. From 0.776 g (2.0 mmol) of **11** and 0.644 g (2.0 mmol) of **2** (E=H)[4] there was obtained 1.02 g (80%) of **6a**, mp 200-203 °C (benzene); ^{1}H NMR δ 3.37 (s, 4 H), 3.54 (s, 4 H), 5.15 (s, 4 H), 6.72 (d, J = 8.8 Hz, 4 H), 6.96 (d, J = 8.8 Hz, 4 H), 7.11 (d, J = 8.3 Hz, 4 H), 7.17 (d, J = 7.7 Hz, 2 H), 7.38-7.50 (m, 8 H), 7.63 (t, J= 1.8 Hz, 1 H); ^{13}C NMR δ 34.4, 34.9, 70.8, 114.8, 119.6, 125.5, 126.7, 127.1, 128.3, 129.2, 129.5, 130.3, 130.5, 137.5, 137.6, 139.6, 141.3, 157.3; mass spectrum, *m/e* (relative intensity) 637 (20, M^+), 361 (8), 350 (29), 348 (30), 318 (28), 288 (100), 258 (96), 243

(69), 212 (96). Anal. Calcd for $C_{41}H_{35}NO_2S_2$: C, 77.20; H, 5.53. Found: C, 77.34; H, 5.46. For **6b:** ^{1}H NMR same as for **6a** except δ 7.38-7.50 (m, 7 H); mass spectrum, *m/e* (relative intensity) 638 (100, M^+).

Cyclophane 6c. From 0.776 g (2.0 mmol) of **11** and 0.802 g (2.0 mmol) of **2 (E = Br)**[4] there was obtained 0.573 g (40%) of **6c** mp 182 °C; ^{1}H NMR δ 3.31 (s, 4 H), 3.40 (s, 4 H), 5.02 and 5.06 (s, 4 H, becomes a singlet at δ 5.00 on heating to 105 °C in toluene-d_6), 6.78-7.20 (m, 22 H); ^{13}C NMR δ 34.52, 34.95, 69.85, 114.82, 118.92, 122.30, 126.80, 127.52, 128.02, 129.28, 129.50, 130.42, 130.81, 137.44, 137.81, 139.88, 141.08, 157.81; mass spectrum (FAB) 718 (M^++2). Anal. Calcd for $C_{41}H_{34}BrNO_2S_2$: C, 68.70; H, 4.78. Found: C, 68.72; H, 5.01.

Cyclophane 7. From 0.776 g (2.0 mmol) of **11** and 0.644 g (2.0 mmol) of **12**[4] there was obtained 0.764 g (60%) of **7**, mp 162 °C; ^{1}H NMR δ 3.58 (s, 4 H), 3.66 (s, 4 H), 5.28 (s, 4 H), 6.83 (d, J = 8.7 Hz, 4 H), 7.09 (d, J = 8.7 Hz, 4 H), 7.26-7.43 (m, 14 H), 7.66 (t, J = 8.2 Hz, 1 H); ^{13}C NMR δ 35.2, 35.7, 69.6, 115.0, 120.8, 125.8, 126.1, 126.2, 127.8, 127.9, 128.0, 128.97, 129.04, 130.2, 130.7, 137.4, 138.7, 141.2, 141.3, 141.5; mass spectrum, *m/e* (relative intensity) 637 (80, M^+), 531 (50), 348 (70), 316 (50), 304 (70), 271 (100), 256 (40), 241 (60). Anal. Calcd for $C_{41}H_{35}NO_2S_2$: C, 77.20; H, 5.53. Found: C, 77.32; H, 5.49.

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6. Due to retirement (H. H.) we are unable to continue these studies; others are welcome.
7. For general procedures, see Vinod, T. and Hart, H., *J. Org. Chem.* **1990**, *55*, 881-890; Vinod, T.K. and Hart, H., *J. Org. Chem.* **1991**, *56*, 5630-5640.

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