A Novel Synthesis of Hemispherands

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Abstract: A novel, flexible synthesis of hemispherands (2,5,8-tri-tertiary(9,3,3')-m-terphenylophane) 5a–d) with different central aromatic groups is described. The key step comprises the introduction of the central aromatic ring in the last step of the synthesis via a Suzuki cross-coupling reaction using palladium tetrakis(triphenylphosphine) as a catalyst and sodium or potassium cations serving as a template ion in the macrocyclization.

Hemispherands represent an interesting class of host molecules in supramolecular chemistry. The synthesis and the complexation with alkali and alkyl ammonium salts were reported first by Cram et al. In the parent molecule (e.g., 5b) the molecular cavity is composed of a rigid m-teraphenyl moiety in which three oxygen binding sites are conformationally organized prior to complexation, and a flexible polyether chain. Cram et al. also published hemispherands composed of three or four anilin units or anilin and cyclic urea units. In our laboratories we developed strategies for the synthesis of hemispherands with a modified central aromatic ring. This aromatic ring could be introduced either by using pyrylum salt chemistry or condensation of an incorporated dibenzyl ketone moiety with nitromalonodialdehyde. In this paper we present our preliminary results on a novel, flexible synthesis of this type of compound in which the central aromatic ring is introduced in the last step of the synthesis via a Suzuki coupling using a Pd(0) catalyst.

The reaction sequence is summarized in Scheme 1. Reaction of the easily accessible 2-bromo-6-(chloromethyl)-4-methylnisole (I) (prepared in two steps from 4-methylnisole) with diethylene glycol in THF in the presence of NaH as a base afforded compound 2 as a colorless oil in 83% yield after bulb to bulb distillation (bp 160–170 °C, 5 × 10⁻² mm Hg). Compound 2 was transformed in the diboronic acid 3 upon treatment with n-BuLi in THF followed by reaction of the resulting dillithio compound with trimethyl borate and subsequent treatment with 3% HCl. Diboronic acid 3 could not be purified on account of slow decomposition and was therefore used as such in the macrocyclization step. Aryl dibromides 4a–d were obtained in high yields from commercially available phenols by alkylation with methyl iodide or allyl bromide. Crude diboronic acid 3 was subjected to modified Suzuki cross-coupling conditions (toluene/toluene 1:1, Me3P, reflux) with aryl dibromides 4a–d to give the

![Scheme 1](image-url)
hemi-spherands 5a-d after chromatography in 12-21% yield (calculated on 2) (Table 1). Hemispherands 5a-d were purified as their potassium complexes by chromatography using silica gel mixed with KBr.

In a similar way, macrocycle 6 containing two o,o'-dianisyl units was obtained in 18% yield starting from 2 and the corresponding diboronic acid 3 (Scheme 2).

\[
\text{Pd(PPh}_3\text{)₄; Na}_2\text{CO}_3 / \text{PhMe} / H_2O \\
14\text{h reflux} \\
18\%
\]

Scheme 2

<table>
<thead>
<tr>
<th>compd</th>
<th>yield(%)</th>
<th>mp (°C)</th>
<th>lit mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>14</td>
<td>191-193</td>
<td>192-193⁹</td>
</tr>
<tr>
<td>5b</td>
<td>15</td>
<td>208-210</td>
<td>208-209²</td>
</tr>
<tr>
<td>5c</td>
<td>21</td>
<td>133-135</td>
<td></td>
</tr>
<tr>
<td>5d</td>
<td>12</td>
<td>151-152.5</td>
<td>150-152⁹</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>117-119</td>
<td>116-119⁹</td>
</tr>
</tbody>
</table>

*calculated on 2.

In order to investigate the possible role of the cation and the catalyst, the reaction of 3 with 4c to give 5c was carried out under different conditions (Table 2). Variation of the cation (Li⁺, Na⁺, K⁺, Cs⁺; entries 1-4) indicates that Na⁺ and K⁺ probably serve as a template ion in the macrocyclization reaction. A Pd(0) catalyst appears to be superior to a Ni²⁺ one (entries 3, 6, 7).

Although the yields of the hemispherands 5a-d are still moderate, we feel that the described approach can compete with other methods because of its limited number of reaction steps and its flexibility.

**Representative macrocyclization procedure**

A solution of aryl dibromide 4c (0.31 g, 1.0 mmol) and crude diboronic acid 3 (0.46 g, 1.0 mmol) in 95% EtOH (5 mL) was added to a vigorously stirred, hot mixture of tetrakis(triphenylphosphine)-palladium(0) (23 mg, 0.02 mmol) and Na₂CO₃ (50 mL, 2M eq solution) in toluene (50 mL). The mixture was refluxed for 14 h and subsequently cooled to room temperature. After separation of the layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with 1N HCl (3 x 10 mL) and water (20 mL). After evaporation of the solvents, the residue was dissolved in MeOH (15 mL) and stirred for 1 h with a saturated methanolic KBr solution (15 mL). After removal of the MeOH the residue was flash chromatographed (v/v SiO₂-KBr, 10:1). The non-ionic impurities were eluted with CH₂Cl₂ changing the eluent to CH₂Cl₂-MeOH, 95:5 v/v gave 5c-KBr. The fractions containing 5c-KBr were combined, washed with 3% HCl (3 x 10 mL), water (10 mL), and dried with MgSO₄. After evaporation of the solvent the residue was recrystallized from 95% EtOH to give pure hemispherand 5c as a white solid.

**References and Notes**

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(12) 2. $^1$H NMR (CDCl$_3$) δ 7.50 (d, 2 H, $J = 1.6$ Hz, ArH), 7.29 (d, 2 H, $J = 1.6$ Hz, ArH), 4.58 (s, 4 H, ArCH$_2$O), 3.81 (s, 6 H, OCH$_3$), 3.69 (s, 8 H, OCH$_2$CH$_2$O), 2.27 (s, 6 H, CH$_3$); mass spectrum (EI). $m/e$ 530.024 (M$^+$, calculated for C$_{20}$H$_{28}$Br$_2$O$_5$ 530.030).

(13) 5c. $^1$H NMR (CDCl$_3$) δ 7.24 (s, 2 H, ArH, inner), 7.06 (s, 4 H, ArH, outer), 5.0-4.8 (m, 1 H, -CH=CH$_2$), 4.72 and 4.41 (ABq, 4 H, $J = 11.6$ Hz, ArCH$_2$O), 4.63-4.56 and 4.47-4.40 (m, 2 H, =CH$_2$), 3.75-3.5 (m, 8 H, OCH$_2$CH$_2$O), 3.38 (s, 6 H, OCH$_3$).

3.25 (d, 2 H, $J = 6.3$ Hz, OCH$_2$-CH=), 2.45 (s, 3 H, CH$_3$ inner), 2.32 (s, 6 H, CH$_3$ outer); mass spectrum (FAB, 3-nitrobenzyl alcohol as a matrix). $m/e$ 541 (100%; [M + Na$^+$]). Anal. Calc'd for C$_{32}$H$_{34}$O$_6$: C, 74.10; H, 7.58. Found: C, 73.88; H, 7.32.

(14) Using KBr/E$_3$N/DMF and 2% Pd(PPh$_3$)$_4$ gave hemispherand 5c in a yield of 38%. Unfortunately this yield could not always be reproduced.