Reduction of Pseudo-geminal Bis(ethynyl)-Substituted [2.2]Paracyclophanes

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Abstract The reduction of pseudo-geminal bis(ethynyl)-substituted [2.2]paracyclophanes provides compounds with new bridges. The type of bridging is substituent dependent. The (trimethylsilyl)ethynyl moiety induces the formation of a bridge with two semicyclic double bonds; less bulky substituents, like propynyl and phenylethynyl, lead to bridges with endo double bonds.

Key words acetylenes, reduction, dienes, lithium, paracyclophanes

[2.2]Paracyclophane derivatives have been the subject of particular interest since their first appearance in the literature more than six decades ago.\textsuperscript{1--3} Since then, most studies have been devoted to elucidation of the structural characteristics of [2.2]paracyclophanes, particularly their geometry and steric properties, transanular interactions, and ring strain.\textsuperscript{4--6} As far as the chemical behavior is concerned the vast majority of the reported reactions has been carried out at the benzene rings. The chemistry of the molecular bridges of these molecules should also be interesting, especially when the bridges carry important functional groups. In the last several years we have developed several methods for the introduction of new bridges into [2.2]paracyclophanes.\textsuperscript{7} Although we reported the incorporation of various functional groups into the ethano bridges of [2.2]paracyclophanes,\textsuperscript{8} the chemistry of this type of bridge has received little attention so far.

Functional groups in pseudo-geminally substituted [2.2]paracyclophanes often undergo highly specific reactions. This is due to the rigid framework and the short distance within the aromatic units. In one such application, unsaturated cyclophane bis(esters) provided the corresponding ladderanes by intramolecular photocyclization.\textsuperscript{9--11} The 4,13-bis(ethynyl)[2.2]paracyclophane and its derivatives are interesting building blocks for molecular scaffolding,\textsuperscript{12} since the ethynyl functions can easily be connected by various coupling reactions.

Pentalenes represent another class of hydrocarbons with an impressive chemical history.\textsuperscript{13} The development of the chemistry of these antiaromatic 4n hydrocarbons was strongly correlated with the number of efficient synthetic methods for the preparation of these compounds. A general route to dibenzopentalenes is represented by the metal-induced dimerization of different types of ethynyl aromatics.\textsuperscript{14} For example, the reduction of tris(isopropyl)siyllethynylbenzene (1) with excess lithium, followed by oxidation with iodine provided the dibenzo[a,e]pentalene derivative 2 in 7% yield (Scheme 1).\textsuperscript{15}

Prompted by these recent developments on the chemistry of pentalenes, we decided to investigate the reactions of a series of pseudo-geminally substituted bis(ethynyl) derivatives with lithium. Thus, we are presenting here a preliminary report on the interaction of lithium with 4,13-bis(trimethylsilyl)-, 4,13-bis(propyn-1-yl)-, and 4,13-bis(phenylethynyl)[2.2]paracyclophanes.

In a first experiment we have used as substrate an ethynyl aromatic compound related to 1, 4,13-bis(trimethylsilyl)\textsuperscript{[2.2]paracyclophane (3)}\textsuperscript{[1]} While the reaction described in Scheme 1 was performed using almost fivefold excess of lithium for one triple bond we decided to use a double amount for our substrates. For instance, by adding a tenfold excess of lithium powder to a solution of 3 in dry THF at 0 °C we obtained only compound 4, in 25% isolated yield, along with some intractable material (Scheme 2).\textsuperscript{[16]}}
The structure of this compound has been assigned on the basis of 2D NMR studies and mass spectrometric analysis. The NMR spectra clearly indicate a symmetrical structure; a possible second isomer with the trimethylsilyl groups both pointing to the interannular space can be ruled out because of the steric hindrance between these two bulky groups. The mechanistic route for the formation of diene 4 might be considered similar to that for dibenzopentalene 2. However, due to the proximity of the two triple bonds, the intermediate anion radicals usually formed in a Birch-type reduction prefer an intramolecular (benzylic) coupling instead of an intermolecular one, as in the case of 2. The intermolecular interaction between intermediate species cannot be ruled out. Moreover, these reactions might be responsible for the intractable material as polymerization can easily take place via these interactions.

Further investigations were carried out with 4,13-bis(propyn-1-yl)[2.2]paracyclophane (5a) and 4,13-bis(phenylethylnyl)[2.2]paracyclophane (5b), respectively. Thus, following the general procedure described for 3,16 the reaction of 5a with ten equivalents of lithium reached completion in two hours (TLC monitoring). Separation of the crude mixture by preparative TLC provided compounds 6a, 7a, and 8 in 31% overall isolated yield, along with intractable material (Scheme 3). The structures of these compounds were assigned by 2D NMR spectroscopic and mass spectrometric analyses. The 1H NMR spectrum of 6a show the signals corresponding to a new methylene group as an AB quartet (δ = 2.7 and 3.7 ppm) and only one singlet corresponding to six protons. Again, the 1H NMR spectrum indicate a symmetrical compound. The two-dimensional correlations corrobo-rated this proposal which is also supported by the mass spectra where the molecular ion corresponds to the formula of C22H24 (288 a.m.u.) for 6a.17

Surprisingly, the 1H NMR spectrum of compound 7a indicated the disappearance of the characteristic pattern of the paracyclophane unit; the signals for the aromatic region were shifted to lower fields (to ca. δ = 7 ppm), and the crowded aliphatic area of the ethano bridges was missing.18 These data, accompanied by signals for two methyl groups, plus the mass spectrometric information prompted us to propose the structure shown in Scheme 3. Supplementary structural information is provided below. The 1H NMR spectrum of 8 also indicated the missing [2.2]paracyclophane core. Moreover, the structure is symmetrical and contains three different methyl groups.19

Although the total isolated yields are good in comparison with the yield reported for dibenzopentalene 2, we decided to investigate the influence of the amount of excess lithium on overall yields and on the composition of reaction products. Thus, we performed the same reactions using fivefold excess and twofold excess lithium, respectively. The reaction of 4,13-bis(trimethylsilyl)[2.2]paracyclophane (3) with five equivalents and 2 equivalents of alkali metal. Again, the total yields and the reaction time have increased by reducing the amount of lithium (Table 1, entries 5 and 6, respectively). While the yields for compounds 6a and 6b are higher than the yield obtained in the presence of ten equivalents of lithium, the amount of the linear compound 8 is slightly lower. This suggests the possibility of controlling the distribution of the reaction products by a slower generation of the reactive intermediates during the reduction process.

On first sight, the formation of compounds 4 and 6 appears to be contradictory. While the electron transfer to the triple bonds of 3 leads to an anion radical, with the free rad-
with two trimethylsilyl groups in a bis(ethynyl) derivatives located at the benzylic position (Scheme 4, path b), the first step consists in ethano bridge breaking an intermediates. Thus, when the second ethano bridge also may undergo homolysis and, probably, its products are contained in the reaction mixture supports the formation of diene 4. Furthermore, the isolation of linear compound 8 from the reaction mixture supports the formation of diene 7 by a mechanism which involves in the first step the break of an ethano bridge. It also supports the preference for breaking the ethano bridge situated next to the pseudo-geminal substituents. The second ethano bridge also may undergo homolysis and, probably, its products are contained in the first step may consists in the formation of 9 by diradical interactions. In the second step, intermediate 9 or its anion radicals suffers the break of the ethano bridge with subsequent formation of 11 (Scheme 4, path d). In fact, compounds 7 and 11 are rotamers and, apparently as drawn in Scheme 4, both have a plane of symmetry. Due to the lack of crystallographic data we decided to investigate the formation of the two rotamers by means of theoretical studies. Thus, DFT [B3LYP-D3/6-311++G(d,p)] calculations indicated that compound 7 is more stable than compound 11, the difference between the minimum energies being 7 kcal/mol. Moreover, as shown in Figure 1, compound 11 is significantly distorted. The lack of symmetry for this compound is inconsistent with the NMR spectra of the isolated product.

Table 1

Reduction of Pseudo-geminal Bis(ethynyl)-Substituted [2.2]Paracyclophanes with Different Amounts of Lithium

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Lithium (equiv)</th>
<th>Reaction time (h)</th>
<th>Yield of reaction products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10</td>
<td>12</td>
<td>4 (25)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>48</td>
<td>4</td>
<td>25 (28)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>80</td>
<td>4</td>
<td>29 (29)</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>10</td>
<td>2</td>
<td>6a (10) + 7a (11) + 8 (10)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>16</td>
<td>6a (14) + 7a (12) + 8 (8)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>32</td>
<td>6a (15) + 7a (13) + 8 (7)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5b</td>
<td>10</td>
<td>8</td>
<td>6b (15) + 7b (17)</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>24</td>
<td>6b (17) + 7b (17)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>48</td>
<td>6b (19) + 7b (18)</td>
<td></td>
</tr>
</tbody>
</table>

Due to the lack of crystallographic data we decided to investigate the formation of the two rotamers by means of theoretical studies. Thus, DFT [B3LYP-D3/6-311++G(d,p)] calculations indicated that compound 7 is more stable than compound 11, the difference between the minimum energies being 7 kcal/mol. Moreover, as shown in Figure 1, compound 11 is significantly distorted. The lack of symmetry for this compound is inconsistent with the NMR spectra of the isolated product.

Figure 1  The optimized structures of rotamers 7 (left) and 11 (right) according to DFT calculations.
intractable material. Most likely, the two extra ethylidene fragments in 8 originate from the interactions between the reactive intermediates. The source of hydrogen atoms necessary for the formation of the reaction products might also be a molecule of another intermediate, although the solvent and/or workup conditions should not be excluded.

The reaction of 4,13-bis(phenylethynyl)[2.2]paracyclophane (5b) with ten equivalents of lithium provided only compounds 6b and 7b (Table 1, entry 7). The absence of cleavage products such as 8 may be caused by the replacement of the methyl by the phenyl substituent at the triple bond. In the latter case all intermediates gain stability due to the additional benzylic resonance. The reaction of 5b with five equivalents and two equivalents of lithium provided the same reaction products 6b and 7b. As in the previous experiments, the decreasing of the amount of excess lithium has resulted in a significant increasing of the reaction time and only a slight improvement of the isolated yields (Table 1, entries 8 and 9).

In conclusion, we report a substituent-dependent reduction of pseudo-geminal bis(ethynyl)-substituted [2.2]paracyclophanes. The (trimethylsilyl)ethynyl group induces the formation of a bridge with two semicyclic double bonds; less bulky substituents, such as propynyl and phenylethynyl, lead to bridges with endo double bonds. The role of the solvent and the concentration of the substrate on the nature and composition of the reaction products are under investigation.

Acknowledgment
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References and Notes

(2) Cram, D. J.; Steinberg, H. J. Am. Chem. Soc. 1951, 73, 5691.
(16) Typical Procedure
To a solution of 4,13-bis(trimethylsilyl) [2.2]paracyclophane (3, 167 mg, 0.4 mmol) in dry THF (10 mL) was added powdered lithium (28 mg, 4 mmol). The reaction mixture was stirred at r.t. until the starting material had been consumed (12 h, TLC monitoring). Filtration through Celite followed by evaporation under vacuo gave the crude product that was purified by column chromatography to provide compound 4 as a colorless solid (40 mg, 25%); Rf = 0.59 (CH2Cl2–pentane, 1:5); mp 167–170 °C. In conclusion, we report a substituent-dependent reduction of pseudo-geminal bis(ethynyl)-substituted [2.2]paracyclophanes. The (trimethylsilyl)ethynyl group induces the formation of a bridge with two semicyclic double bonds; less bulky substituents, such as propynyl and phenylethynyl, lead to bridges with endo double bonds. The role of the solvent and the concentration of the substrate on the nature and composition of the reaction products are under investigation.

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