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

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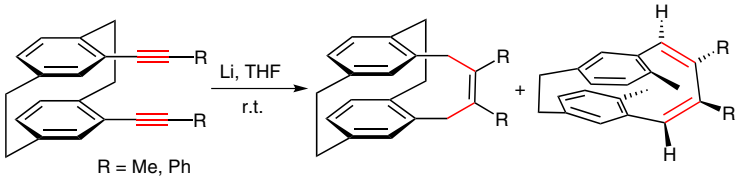

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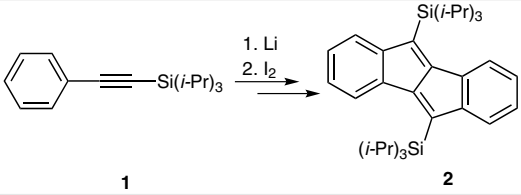
Abstract The reduction of pseudo-geminal bis(ethynyl)-substituted [2.2]paracyclophanes provides compounds with new bridges. The type of bridging is substituent dependent. The (trimethylsilyl)ethynyl moiety induces the formation of a bridge with two semicyclic double bonds; less bulky substituents, like 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.[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.[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.[7] Although we reported the incorporation of various functional groups into the ethano bridges of [2.2]paracyclophanes,[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.[9–11] The 4,13-bis(ethynyl)[2.2]paracyclophane and its derivatives are interesting building blocks for molecular scaffolding,[12] since the ethynyl functions can easily be connected by various coupling reactions.

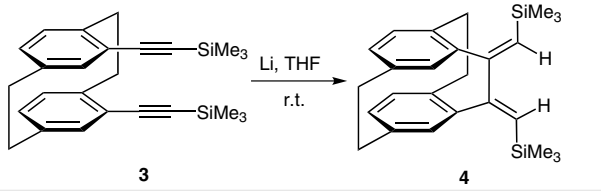
Pentalenes represent another class of hydrocarbons with an impressive chemical history.[13] The development of the chemistry of these antiaromatic 4n hydrocarbons was strongly correlated with the number of efficient synthetic methods for the preparation of these compounds. A general route to dibenzopentalenes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



Scheme 1

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)[2.2]paracyclophane (**3**). 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).[16]



Scheme 2

The structure of this compound has been assigned on the basis of 2D NMR studies and mass spectrometric analysis.[16] 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.

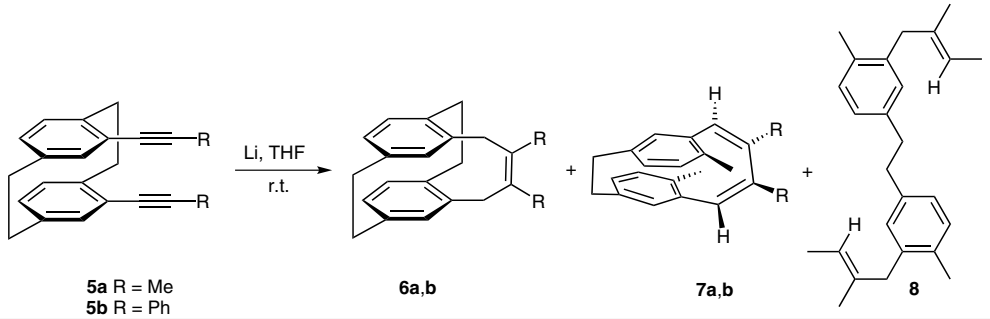
Further investigations were carried out with 4,13-bis(propyn-1-yl)[2.2]paracyclophane (**5a**) and 4,13-bis(phenylethynyl)[2.2]paracyclophane (**5b**), respectively. Thus, following the general procedure described for **3**,[16] the reaction of **5a** with ten equivalents of lithium reached completion 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 ^{1}H 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 ^{1}H NMR spectrum indicate a symmetrical compound. The two-dimensional correlations corroborated this proposal which is also supported by the mass spectra where the molecular ion corresponds to the formula of $C_{22}H_{24}$ (288 a.m.u.) for **6a**.[17]

Surprisingly, the ^{1}H 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 ^{1}H 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 lithium provided the same reaction product with slight improving of the isolated yields (Table 1, entries 2 and 3, respectively). However, a significant increasing of the reaction time has been recorded with the decreasing of the amount of lithium. Similar results were obtained from the reaction of 4,13-bis(propin-1-yl)[2.2]paracyclophane (**5a**) with five equivalents and two 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-



Scheme 3

Table 1 Reduction of Pseudo-geminal Bis(ethynyl)-Substituted [2.2]Paracyclophanes with Different Amounts of Lithium

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

ical located at the benzylic position (Scheme 4, path b), bis(ethynyl) derivatives **5** undergo electron transfer to the triple bonds in an opposite way (Scheme 4, path a). Stepwise, this should lead to intermediate **9** which presents a new butadiene bridge between the pseudo-geminal positions. Most likely, this type of bridging induces considerable strain in the molecule. For this reason, intermediate **9** undergoes further reduction leading to compounds **6**, which possess a more flexible third bridge. The reaction pathway a it is not excluded for 4,13-bis(trimethylsilyl)[2.2]paracyclophane (**3**). However, it will lead eventually to a double bond with two trimethylsilyl groups in a *cis* configuration; definitely, this will be a highly strained substance. Thus, for thermodynamic reasons, the reduction of paracyclophane derivative **3** ends with production of the butadiene **4**.

The reaction mechanism for the formation of compounds **7** has literature background with respect to the breaking of the ethano bridge. The Birch reduction of [2.2]paracyclophane, under specific reaction conditions, resulted in the cleaved product, 4,4′-dimethylbibenzyl.[20] Despite of this reference an important mechanistic issue still remains. The competition between ethano bridge breaking and bridge formation by diradical interaction controls the stereochemistry of the reaction product. Thus, when the first step consists in ethano bridge breaking an intermediate of type **10** should be formed (Scheme 4, path c). This first step may occur either on the substrate or on the anion radicals derived therefrom. The free rotation around the second bridge is followed by the second step in which butadiene bridge formation leads to compounds **7**. Alternatively, 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.

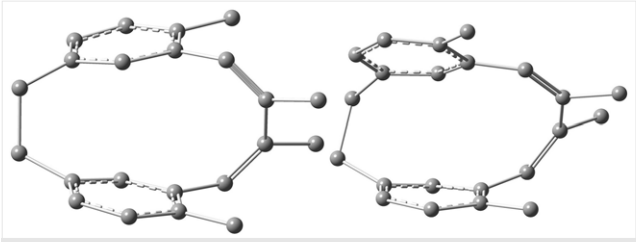
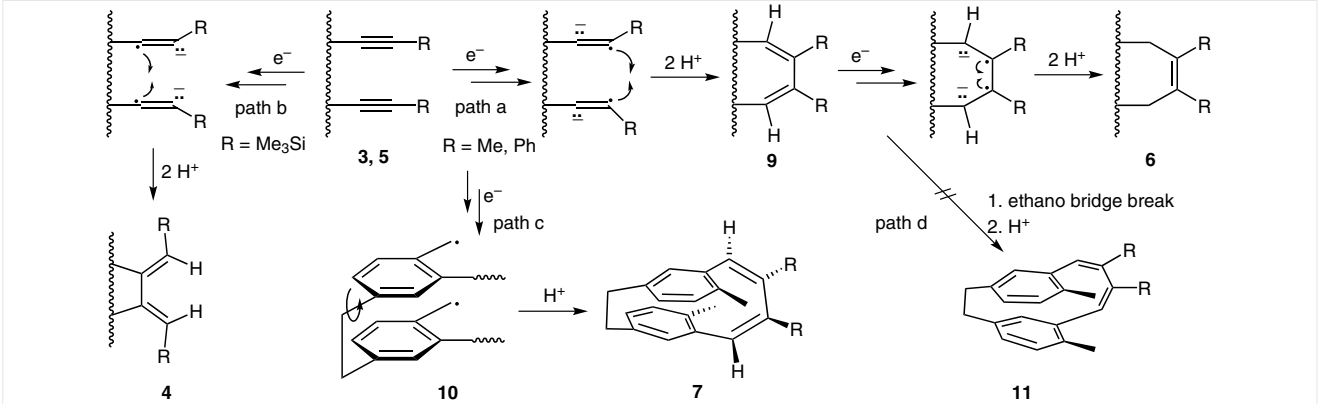


Figure 1 The optimized structures of rotamers **7** (left) and **11** (right) according to DFT calculations

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



Scheme 4

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 do 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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(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%); R_f = 0.59 (CH_2Cl_2–pentane, 1:5); mp 125–126 °C. IR (ATR): 2981, 1545, 1311, 914, 857, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.11 (s, 18 H, 6 CH_3), 2.65 (m, 2 H, CH_2), 3.05 (m, 6 H, 3 CH_2), 6.19 (d, ^4J = 2.1 Hz, 2 H, 2 CH_{ar}), 6.34 (d, ^3J = 8.1 Hz, 2 H, 2 CH_{ar}), 6.44 (dd, ^3J = 8.1 Hz, ^4J = 2.1 Hz, 2 H, 2CH_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 0.2, 32.7, 36.2, 120.2, 130.4, 132.5, 139.1, 139.4, 139.9, 143.6, 158.7 ppm. MS (EI): *m/z* (%) = 402 (65) [M^+], 73 (100).
(17) **Spectral Data of 6a**
Colorless solid, 15 mg, 10%; R_f = 0.4 (CH_2Cl_2–pentane, 1:10); mp 142–143 °C. IR (ATR): 2954, 1575, 1451, 1333, 1211, 870, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.05 (s, 6 H, 2 CH_3), 2.7 and 3.7 (ABq, ^2J = 10.4 Hz, 4 H, 2 CH_2), 2.90 (m, 2 H, CH_2), 2.98 (s, 4 H, 2 CH_2), 3.58 (m, 2 H, CH_2), 6.20 (d, ^4J = 2.2 Hz, 2 H, 2 CH_{ar}), 6.27 (dd, ^3J = 8.0 Hz, ^4J = 2.2 Hz, 2 H, 2 CH_{ar}), 6.35 (d, ^3J = 8.0 Hz, 2 H, 2 CH_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 23.2, 32.0, 35.2, 37.4, 130.5, 130.8, 132.5, 134.0, 136.5, 139.5, 140.3 ppm. MS (EI): *m/z* (%) = 288 (20) [M^+], 169 (100).
(18) **Spectral Data of 7a**
Pale yellow solid, 16 mg, 11%; R_f = 0.64 (CH_2Cl_2–pentane, 1:10); mp 138–139 °C. IR (ATR): 2934, 1551, 1420, 1341, 1201, 845, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.13 (s, 6 H, 2 CH_3), 2.30 (s, 6 H, 2 CH_3), 3.06 (m, 4 H, 2 CH_2), 6.12 (s, 2 H, 2 CH), 7.05 (m, 6 H, 6 CH_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 19.4, 19.6, 38.2, 126.5, 126.9, 128.6, 130.4, 135.8, 136.5, 138.4, 141.2 ppm. MS (EI): *m/z* (%) = 288 (23) [M^+], 171 (100).
(19) **Spectral Data of 8**
Pale yellow solid, 17 mg, 10%; R_f = 0.56 (CH_2Cl_2–pentane, 1:10); mp 133–134 °C. IR (ATR): 2917, 1547, 1412, 1301, 1218, 931, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.72 (s, 6 H, 2 CH_3), 2.32 (s, 6 H, 2 CH_3), 2.37 (s, 6 H, 2 CH_3), 2.61 (s, 4 H, 2 CH_2), 3.38 (s, 4 H, 2 CH_2), 6.35 (s, 2 H, 2 CH), 6.87 (dd, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 2 H, 2 CH_{ar}), 6.98 (d, ^3J = 7.7 Hz, 2 H, 2 CH_{ar}), 7.05 (d, ^4J = 1.8 Hz, 2 H, 2 CH_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 19.4, 20.1, 20.9, 37.1, 38.0, 126.1, 127.0, 128.8, 129.8, 132.7, 133.5, 136.2, 138.0 ppm. MS (EI): *m/z* (%) = 346 (2) [M^+], 171 (100).
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