A New Way to Generate Functionalized Bridges in [2,2]Cyclophanes

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Abstract: The synthesis of valuable precursors of cyclic endiynes has been accomplished by base-catalyzed intramolecular cyclization of pinacolone-type compounds.

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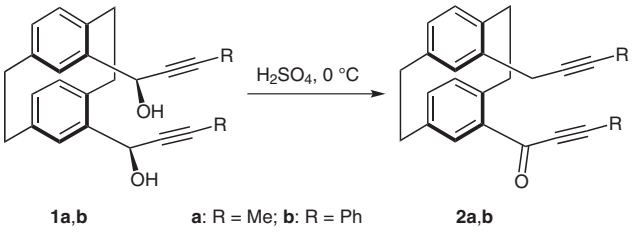
[2,2]Paracyclophanes constitute an intriguing class of compounds that have attracted a constantly growing interest since their first appearance in the chemical literature exactly 60 years ago.[1–3] Most studies so far concern the structural characteristics of [2,2]paracyclophanes, particularly its geometry and its steric properties, transanular interactions, and ring-strain; the electronic interaction between the aromatic rings having a sandwich form, their influence on reactivity in electrophilic aromatic substitution reactions, and their implications for charge-transfer complex formation have also been investigated.[4–6] As far as the chemical behavior is concerned, the vast majority of the reported reactions have been carried out at the benzene rings. However, the chemistry of the molecular bridges of these molecules should also be interesting, especially when the bridges carry important functional groups. Whereas we have previously described the introduction of various functional groups into the ethano bridges of [2,2]paracyclophanes[7] and the generation of new types of unsaturation by isomerization,[8] we now report on a novel process which not only generates a new bridge in a *pseudo-geminally* substituted [2,2]paracyclophane, but also produces new, and possibly widely usable functionality in this new bridge simultaneously. In *pseudo-geminally* substituted [2,2]paracyclophanes the functional groups are often held in such a position as to allow highly specific reactions to take place between them in near quantitative yield. In one such application, unsaturated cyclophane bis-esters undergo intramolecular photocyclization to the corresponding ladderane isomers.[9]

Rather interesting chemical behavior has arisen from the combination of [2,2]paracyclophane structures with bispropargylic or bisallenic systems.[10,11] It is known that in a crystal of [2,2]paracyclophane, the distance between the *pseudo-geminal* carbon atoms is only 3.09 Å.[12] On the other hand, Nicolaou postulated the critical upper limit for the distance between the terminal acetylenic carbons required for cyclization of conjugated endiynes (Bergman cyclization; related to calicheamicins and esperamicins at a measurable rate at room temperature) to be 3.2–3.3 Å.[13] Later, Gleiter et al. extended these studies to nonconjugated cyclic diynes of medium ring size.[14,15]

In a previous paper we presented a vinylogous pinacol–pinacolone rearrangement that takes place despite the fact that the two hydroxyl groups are formally separated by seven bonds.[16] The reaction involved a transannular hydride shift that occurs between the benzylic positions of the various *pseudo-geminally* substituted [2,2]paracyclophanes (e.g. Scheme 1, **1b** → **2b**).



Scheme 1

Pinacolone type compounds **2** are versatile starting materials for the investigation of intramolecular interactions between propargylic/allenic moieties. The treatment of **2** with an appropriate base should trigger the isomerization of a propargylic into an allenic substituent. We wish to report here on base-induced intramolecular interactions in pinacolone type compounds **2**.

Pinacolone **2a** was synthesized from the corresponding *pseudo-geminal* bispropargylic alcohol **1a** in 83% yield. The latter was obtained by treatment of 4,13-bisformyl[2,2]paracyclophane with 1-propynyl magnesium bromide.[17] The influence of a variety of bases on **2** has been investigated. In the presence of *n*-BuLi or LDA, decomposition of the substrate occurs even below –40 °C. DBU was eventually found to be the base of choice; its reaction in DMSO at ambient temperature occurred smoothly and could easily be monitored by NMR spectroscopy (Scheme 2). Thus, reaction of **2b** with one equivalent of DBU in DMSO was complete in four hours at room temperature. Usual work-up with dichloromethane extraction followed by fractional precipitation with ether and pentane leaves a solution of pure **3b** in 42% isolated yield. The structure of compounds **3** have been unambiguously determined by 2D NMR spectroscopy.[18]

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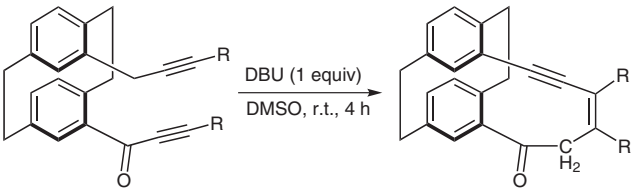
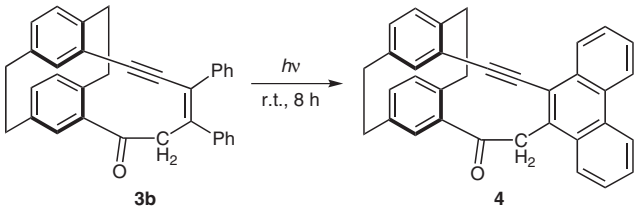


Scheme 2

For the mechanism of this surprising cyclization, we propose that, under the reaction conditions, the first step involves the isomerization of the propargylic group into an allenic substituent. However, although the reaction in $CDCl_3$ is considerably slower than in DMSO (days), NMR monitoring in the former solvent does not reveal the characteristic patterns of this functional group. The intramolecular interaction between the two parallel *pseudo-geminal* substituents appears to be a fast process, which is followed by a 1,5-hydrogen shift, as shown in Scheme 3. This symmetry-allowed process finds an analogy in the thermal isomerization of 1,2,4-pentatriene (vinylallene) to (*Z*)-pent-1-yn-3-ene.[19]

This unexpected rearrangement has provided a valuable starting material for cyclic endiynes. Under appropriate conditions, water elimination from compound **3** should provide, at least as an intermediate, a cyclic endiyne where the distance between terminal acetylenic carbon atoms is below the critical limit postulated by Nicolaou.

Moreover, the particular structure of **3b** can also serve as precursor for generating novel polycyclic hydrocarbons. The use of the stilbene-phenanthrene photocyclization[20] will create a novel bridge consisting of a condensed aromatic system. This photocyclization step has been carried out by irradiating **3b** (10^{-3} M in toluene) in the presence of iodine (0.1 equiv) and biacetyl (2.5 equiv) with a TQ 150 high-pressure mercury lamp (Scheme 4).[21,22] The structure of compound **4**, which was isolated in 23% yield, has again been unambiguously proven by 2D NMR analysis.[23] After photolysis, the overlapping aromatic signals of the phenyl substituents of **3b** were replaced by the characteristic ^{1}H NMR spectrum of a 9,10-disubstituted phenanthrene (δ = 7.5–8.85 ppm, 8 H). The mass spectrum of **4** also confirmed the presence of the new phenanthrene bridge. Normally, in [2.2]paracyclophanes the base peaks correspond to the half molecular mass. In the case of **3b** (*m*/*z* [M^+] calcd for $C_{34}H_{26}O$ = 450), the two fragments resulting from separation of the two ethano bridges and the double bond, provide peaks at *m*/*z* = 217 and 233, with more than 95% relative intensity. In contrast, the mass spectrum of **4** revealed very small peaks for the corresponding molecular units (relative intensity <5%). Most likely, the third phenanthrenic bridge inhibits the cleavage of the phane into two similar halves.



Scheme 4

In conclusion, we have synthesized valuable precursors for cyclic endiynes by a new intramolecular base-induced 1,5-hydrogen shift of a readily available *pseudo-geminally* substituted [2,2]paracyclophane. Investigations into the synthesis and stability of the cyclic endiynes, as well as the alternative synthesis of orthogonal π-systems with fixed double bonds, are underway.

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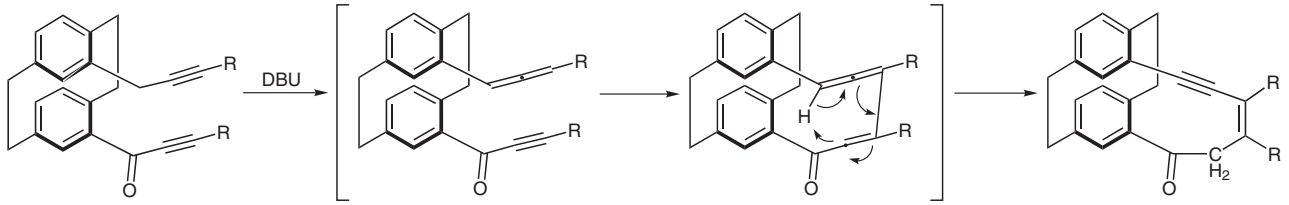

Scheme 3

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(17) Compound **1a**: Yield: 1.2 g (83%); mp 210–211 °C. IR (ATR): 3240, 2922, 2223, 1482, 1261, 1005, 719 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, TMS): δ = 1.71 (d, ^5J = 3.4 Hz, 6 H, 2 × Me), 3.02 (m, 2 H, CH_2), 3.09 (s, 4 H, 2 × CH_2), 3.45 (m, 2 H, CH_2), 4.05 (br s, 2 H, 2 × OH), 5.65 (q, ^5J = 3.4 Hz, 2 H, 2 × CH), 6.52 (m, 4 H, 4 × CH_{Ar}), 6.81 (m, 2 H, 2 × CH_{Ar}). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 3.7 (q), 31.4 (t), 35.1 (t), 61.5 (d), 79.2 (s), 82.1 (s), 127.4 (d), 132.9 (d), 134.6 (s), 135.1 (d), 139.4 (s), 140.1 (s). MS (EI): *m/z* (%) = 326 (22)[$M^+ - H_2O$], 171 (15), 155 (100), 141 (38), 128 (35), 115 (30). Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.76; H, 6.95.
(18) Compound **3b**: Yield: 0.26 g (42%); mp 228–229 °C. IR (ATR): 2925, 1665, 1480, 1314, 1229, 1005, 767, 698 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2, TMS): δ = 2.75 (m, 1 H, CH_2), 2.95 (m, 1 H, CH_2), 2.98–3.30 (m, 4 H, 2 × CH_2), 3.40 (m, 1 H, CH_2), 3.95 (m, 1 H, CH_2), 3.47 and 5.09 (ABq, ^2J = 14.7 Hz, 2 H, CH_2CO), 6.46 (d, ^3J = 7.7 Hz, 1 H, CH_{Ar}), 6.55 (d, ^4J = 2.0 Hz, 1 H, CH_{Ar}), 6.64 (d, ^3J = 7.9 Hz, 1 H, CH_{Ar}), 6.65 (dd, ^3J = 7.7 Hz, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 6.80 (dd, ^3J = 7.9 Hz, ^4J = 2.0 Hz, 1 H, CH_{Ar}), 7.06 (d, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 7.15–7.34 (m, 10 H, 10 × CH_{Ar}). ^{13}C NMR (100 MHz, CD_2Cl_2, TMS): δ = 32.4 (t), 34.0 (t), 34.9 (t), 35.2 (t), 48.7 (t), 99.4 (s), 101.0 (s), 122.2 (s), 126.2 (s), 127.5 (d), 127.6 (d), 128.2 (d, 2 C), 128.6 (d, 2 C), 129.3 (d, 2 C), 129.9 (d, 2 C), 131.1 (d), 132.9 (d), 133.4 (d), 135.2 (d), 137.0 (s), 138.0 (d), 138.3 (d), 139.1 (s), 139.5 (s), 139.9 (s), 140.1 (s), 142.4 (s), 142.5 (s), 150.6 (s), 201.5 (s). MS (EI): *m/z* (%) = 450 (100)[M^+], 317 (32), 303 (35), 233 (98), 217 (95), 191 (18), 131 (28). Anal. Calcd for $C_{34}H_{26}O$: C, 90.63; H, 5.82. Found: C, 90.79; H, 5.75.
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(23) Compound **4**: Yield: 0.1 g (23%); mp 142–143 °C. IR (ATR): 2927, 1663, 1485, 1434, 762, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.77–3.15 (m, 4 H, 2 × CH_2), 3.32 (m, 2 H, CH_2), 3.55 (m, 1 H, CH_2), 3.93 (m, 1 H, CH_2), 4.57 and 5.26 (ABq, ^2J = 15.6 Hz, 2 H, CH_2CO), 6.48 (d, ^3J = 8.0 Hz, 1 H, CH_{Ar}), 6.65 (d, ^4J = 2.0 Hz, 1 H, CH_{Ar}), 6.68 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 6.70 (d, ^3J = 8.2 Hz, 1 H, CH_{Ar}), 6.83 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H, CH_{Ar}), 7.26 (d, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 7.7 (m, 4 H, 4 × CH_{Ar}), 8.22 (dd, ^3J = 7.6 Hz, ^4J = 2.0 Hz, 1 H, CH_{Ar}), 8.39 (dd, ^3J = 7.6 Hz, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 8.72 (dd, ^3J = 8.0 Hz, ^4J = 1.9 Hz, 1 H, CH_{Ar}), 8.78 (dd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1 H, CH_{Ar}). ^{13}C NMR (100 MHz, CD_2Cl_2, TMS): δ = 32.5 (t), 33.74 (t), 33.75 (t), 35.1 (t), 40.5 (t), 97.6 (s), 103.4 (s), 119.7 (s), 122.6 (d), 123.3 (d), 125.1 (d), 126.0 (s), 126.9 (d), 127.1 (d), 127.2 (d), 127.3 (d, 2 C), 129.5 (s), 130.1 (s), 130.6 (s), 131.1 (d), 132.0 (s), 132.9 (d), 133.1 (d), 135.0 (d), 137.8 (d), 137.9 (d), 138.9 (s), 139.0 (s), 139.4 (s), 140.2 (s), 142.1 (s), 142.4 (s), 200.9 (s). MS (EI): *m/z* (%) = 448 (100)[M^+], 405 (24), 315 (43), 302 (25), 131 (18). Anal. Calcd for $C_{34}H_{24}O$: C, 91.04; H, 5.39. Found: C, 91.22; H, 5.27.