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Beckmann rearrangement of cyclotriveratrylene (CTV) oxime: tandem Beckmann-electrophilic aromatic addition

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ABSTRACT

The Beckmann rearrangement has been performed on the oxime of cyclotriveratrylene (CTV) with thionyl chloride affording the ring-expanded 10-membered ring amide exclusively in high yield. Modified conditions afford a helical pentacycle derived from an unusual tandem Beckmann rearrangement and electrophilic aromatic addition followed by demethylation and tautomerization.

The crown-shaped cyclophane cyclotriveratrylene (CTV, **1**, hexamethoxy tribenzocyclononene),[1] has been employed extensively as a scaffold in supramolecular chemistry. This [1.1.1] ortho-cyclophane is readily prepared from the trimerization of veratryl alcohol in acid and has been extensively studied for its capability of binding a variety of smaller organic and organometallic guests within its bowl-shaped cleft.[2–4] Many clathrates of CTV[5–9] and of CTV derivatives[5] have been structurally characterized including clathrates with anionic C70 dimers.[10] Thioether derivatives of CTV have recently been employed to immobilize C60 onto gold surfaces,[11,12] and water soluble CTV derivatives have been developed for biomedical applications including the biological delivery of fullerenes.[13]

We are interested in new apex-modified derivatives of CTV and we recently reported the isolation of the crown and saddle conformers of CTV oxime, and the kinetics of their interconversion.[14] We envisioned performing the Beckmann rearrangement[15,16] on the CTV oxime crown conformer **2** to access the ring-expanded amide and the corresponding amine via reduction to access ring-expanded CTV derivatives that may be functionalized at the apex and are more water soluble. A 9-membered ring azatricyclobenzylene aza-CTV derivative has recently been synthesized in order to assess its pharmacological activity.[17]

We have found that the Beckmann rearrangement performed on pure CTV oxime crown conformer **2** promoted with thionyl chloride in dilute solution at 0 °C proceeds in essentially quantitative yield (99%) with isolation by direct crystallization to afford the new 10-membered ring amide **3**. The ring-expanded amide exists at room temperature exclusively as the crown conformer based on the geminal coupling observed in the proton NMR [4.67 (1H, d, J = 15.0 Hz), 4.44 (1H, d, J = 15.3 Hz), 3.70 (1H, d, J = 15.0 Hz), 3.56 (1H, d, J = 15.3 Hz)], as pseudorotation of the flexible saddle conformation is known to lead to magnetic equivalence of the geminal benzylic methylene protons. Models suggest that the saddle conformer of the amide derivative may not be able to undergo pseudorotation typical of saddle CTV derivatives despite the larger 10-membered ring relative to the 9-membered ring of CTV because of trans-annular steric interactions. Nevertheless, we expect that Beckmann rearrangement of the oxime crown conformer should afford directly the crown conformer of the ring-expanded amide with no opportunity for equilibration to the saddle conformer. Interestingly, the crown conformer of the amide is a structurally chiral molecule, although lacking chiral tetrahedral carbon atoms (Fig. 1).

In the course of studying the Beckmann rearrangement of oxime **2** under certain conditions we observed in addition to amide **3** the unexpected formation of helical pentacycle **4**, resulting from an unexpected tandem Beckmann rearrangement and intramolecular electrophilic aromatic addition (Scheme 1). Pentacycle **4** was produced in good yield (69%) when treating oxime **2** with thionyl chloride in ether/methylene chloride in a more concentrated solution (1 M), along with a small amount of amide **3** (12%). The unique structure of **4** is consistent with spectroscopic and mass spectral analyses. Only five methyls of the original six are observed by

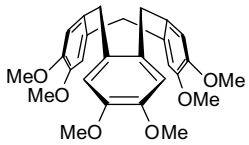

Figure 1. Cyclotriveratrylene, **1** (CTV).

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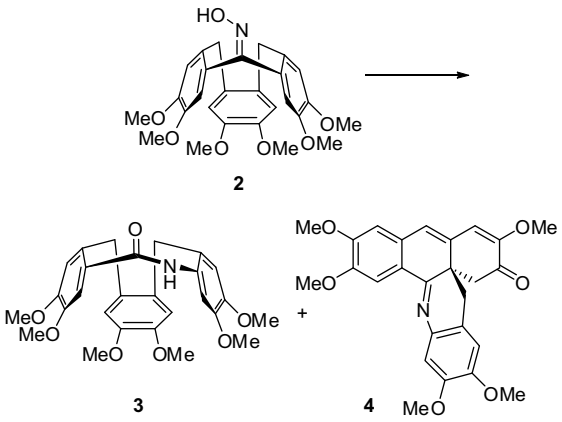


Scheme 1. Beckmann rearrangement of CTV oxime crown conformer to Beckmann amide **3** and tandem Beckmann/electrophilic aromatic addition product **4**.

proton and ^{13}C NMR. A new quaternary carbon atom is observed by DEPT at 39.1 ppm, and a strong carbonyl stretching vibration is observed at 1681 cm^{-1} in the infrared spectrum. A molecular weight of 447 is consistent with the MH^+ ion observed at 448 a.m.u. in the mass spectrum. The structure was ultimately confirmed by single crystal X-ray analysis (Fig. 2).[18] The compound shows an unusual helical arrangement of three 6-membered rings that are all connected at the central carbon atom C6. The helix effectively performs one full turn around C6, and the thread pitch, as defined by the distance of the terminal atoms C2 and C20 of the helix, is 4.98(3) Å. Classic 4-bond W-type coupling of the protons on C1 and C7 is observed for the very rigid pentacyclic system [3.07 (1H, d, J = 16.2 Hz), 2.95 (1H, d(br), J = 16.2 Hz), 2.88 (1H, d, J = 15.9 Hz), 2.34 (1H, dd, J = 15.9, 1.8 Hz)].

Curiously, a solution of tandem product **4** in methylene chloride is ruby red but turns yellow upon shaking with water. The ruby red color then returns upon shaking with brine, and this color change may be repeated, and may reflect reversible addition of water to the electrophilic enone system or to the imine. In the proposed mechanism for the formation of the pentacyclic tandem Beckmann-electrophilic aromatic addition product (Scheme 2), thionyl chloride activates the oxime for the Beckmann rearrangement and the aryl migrates to the oxime nitrogen (structure **5**). The cationic intermediate of the Beckmann rearrangement is represented as a nitrilium cation in structure **6**, since strain on the linear triple bond should be minimal in the 10-membered ring.[19] Cationic intermediate **6** is then attacked by the electron-rich dimethoxyphenyl ring in an electrophilic aromatic addition process forming two new 6-membered rings and the new quaternary center C6. Intermediate **7** might be expected to undergo demethylation of O1, but deprotonation occurs instead forming the conjugated triene **8**. Demethylation of O6 is apparently acid-catalyzed, along with tautomerization involving proton transfer to C1, thus affecting hydrolysis of the enol ether and affording the corresponding conjugated ketone of pentacycle **4** (ν = 1662 cm^{-1}).

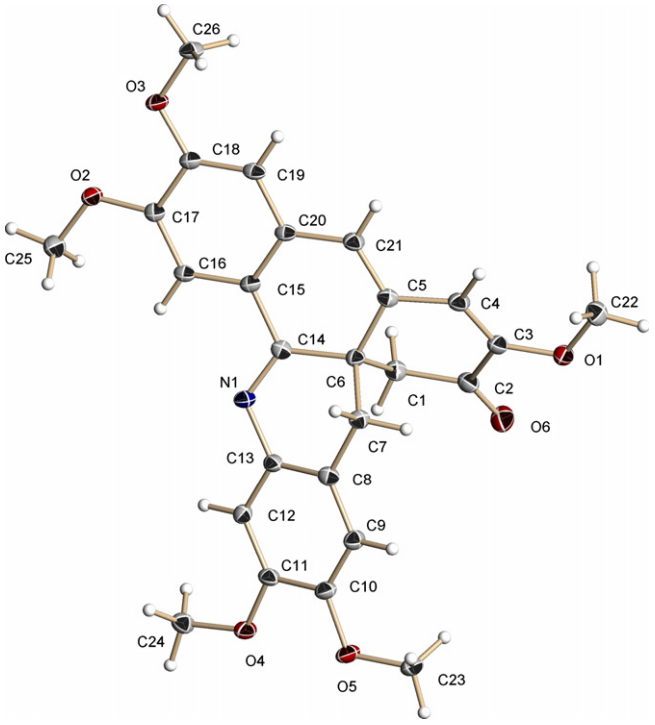
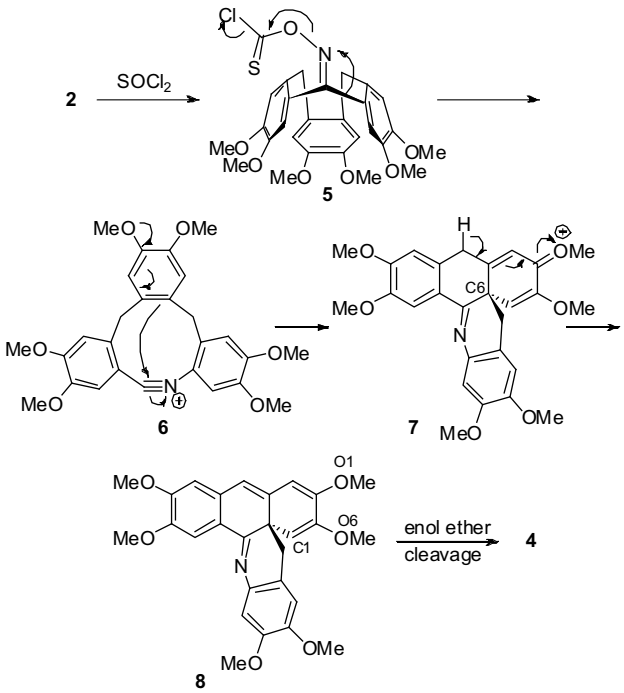


Figure 2. Single crystal X-ray structure of tandem Beckmann/electrophilic aromatic addition product **4**.[18]



Scheme 2. Proposed mechanism of the tandem Beckmann/electrophilic aromatic addition sequence.

The product distribution in the Beckmann rearrangement is dependent upon the reaction conditions. Careful treatment of a dilute (0.01 M) solution of the oxime crown conformer in ether/methylene chloride at 0 °C with neat thionyl chloride (38 equiv) afforded the Beckmann amide in high yield, as noted above. The same reaction under less dilute (0.1 M) conditions gave 60% of Beckmann amide **3** and 28% of the tandem product **4**, whereas

Table 1
Affect of reaction conditions on product distribution of $SOCl_2$ induced Beckmann rearrangement of crown oxime **2**

Concentration (M)	Temperature (°C)	Amide **3** yield (%)	Tandem **4** yield (%)
1.0	0	12	69
0.1	0	60	28
0.01	0	99	0
0.1	−40	42	6
0.1	40	2	48

addition of neat thionyl chloride to a solution of the oxime at 1.0 M afforded the tandem product **4** as the major product in good yield (69%) along with only 12% of the Beckmann amide **3** (Table 1). The pronounced effect of concentration may in part reflect cooling efficiency of the exothermic reaction, favoring the Beckmann amide product in dilute solution held efficiently at 0 °C, and promoting the tandem electrophilic aromatic addition process at more elevated temperatures. Running the reaction at −40°C resulted in a drop in tandem product **4** to only 6%, whereas higher temperatures (40 °C) favors tandem product **4** (48%) over amide **3** (2%).

Treatment of the oxime **2** with acetic anhydride in xylenes with microwave heating to 200–210 °C for 1.5 h under conditions employed by Savarin[20] to produce isoindoles from oximes gave only 26% of amide **3** and none of the tandem product **4**. Heating the oxime **2** to 75 °C for 4 h with toluenesulfonyl chloride and DMAP in pyridine gave a 56% isolated yield of amide **3** and none of tandem-derived product **4**. On the other hand, heating the oxime directly in polyphosphoric acid at 140 °C for 7 min gave pentacycle **4** in 22% yield with none of the Beckmann amide **3**.

Trans-annular electrophilic addition has been observed previously during the oxidation of CTV with sodium dichromate to give a spiro lactone,[21] and Schinzer previously employed nucleophilic allylsilanes to intramolecularly trap the cationic Beckmann rearrangement intermediate in the preparation of various heterocycles,[22–24] but trapping of the cationic Beckmann rearrangement intermediate by electrophilic aromatic addition or substitution has not been previously reported. Thus, this represents a new method for the construction of carbon–carbon bonds. Noteworthy is the construction of a congested quaternary carbon atom. In the CTV system, the nucleophilic addition to the cationic Beckmann intermediate is promoted not only by the electron-rich nature of the veratrole moiety but also by the close proximity of the attacking arene carbon and the nitrilium carbon. Our semi-empirical AM1 calculations suggest that the distance between the attacking veratrole carbon and the nitrilium carbon is 3.4–3.6 Å.

In summary, Beckmann rearrangement of the pure crown conformer of CTV oxime **2** affords either the expected ring-expanded amide **3** or the helical pentacycle **4** which is formed by intramolecular trapping of the cationic Beckmann rearrangement intermediate by the electron-rich arene, or a combination of both products **3** and **4** depending upon the reagents employed as well as the concentration and temperature of the reaction. The tandem Beckmann-electrophilic aromatic addition sequence is potentially very useful, and we are presently exploring the generality of this tandem sequence and its applications in synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.056.

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