A New Method for the Synthesis of Imidazolidinone- and Benzimidazolone-Containing [2.2]Cyclophanes

Keisha K. Ellis, Burkhardt Wilke, Yuegang Zhang, and Steven T. Diver*

Department of Chemistry, State University of New York, Buffalo, New York 14260-3000
diver@acsu.buffalo.edu

Received August 21, 2000

ABSTRACT

A novel acid-catalyzed double nucleophilic addition of bisthiols to heterocyclic bisacetals gives sulfur-containing macrocycles in good yield. Crossover experiments revealed that the acid-catalyzed N-acyl iminium cyclization for the imidazolidinones is reversible. The sulfur atom in the bridge was extruded photochemically, giving new [2.2]heterophanes containing the imidazolidinone and benzimidazolone ring systems. The determined crystal structures for representative members in the benzimidazolone series are also reported.

Cyclophanes have been studied for over a century, and yet interest in these molecules continues due to their structural properties, value as enzyme mimetics, and use in host-guest chemistry. Other recent applications include template-directed synthesis, anion binding, and catalysis. In the [2.2]-cyclophanes, there are no examples that contain an imidazole or imidazolone ring. In the known cases of [2.2]heterophanes, heteroatoms do not occupy the bridgehead position. Our own interest in imidazole-containing cyclophanes is due to their potential applications in metal-binding and catalysis. In this report, we describe a novel approach to imidazolone-containing cyclophanes using an acid-catalyzed double N-acyliminium ion-type macrocyclization (eq 1).

The conventional synthesis of hydrocarbon-derived dithia-cyclophanes utilizes nucleophilic displacement of organic dihalides, e.g., α,α′-dibromo-p-xylene, using bisthiol nucleophiles. When conducted under high dilution conditions, this coupling method has proven successful for the synthesis of dithiacyclophanes; however some cyclophanes are produced in moderate or low yields by this method.
The acetal A can produce a highly electrophilic N-acyl iminium ion under acidic conditions. Prompted by this knowledge, acidic reaction conditions were investigated using \( N,O \)-acetals rather than the corresponding dihalides, which are typically used in the base-catalyzed version of the macrocyclization.\(^9\) Given the propensity of \( N,O \)-acetals to undergo acid-catalyzed transacetalization and that thiolates\(^\text{10}\) tolerate a variety of Brønsted and Lewis acidic conditions, we attempted to prepare macrocycles 4 and 5 using CF\(_3\)-COOH or BF\(_3\)-OEt\(_2\) catalysis in CH\(_2\)Cl\(_2\) solvent (eq 2). The results for the macrocyclization are presented in Table 1.

### Table 1. Macrocyclization via N-Acyl Iminium Ions

<table>
<thead>
<tr>
<th>entry</th>
<th>acetal</th>
<th>dithiol</th>
<th>conditions</th>
<th>product (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3a</td>
<td>1% TFA, reflux (slow add'n)(^b)</td>
<td>4a (40)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3a</td>
<td>1% H(_2)SO(_4), MeOH, rt (slow add'n)(^b)</td>
<td>4a (27)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>3a</td>
<td>50% TFA, reflux (slow add'n)(^b)</td>
<td>5a (43)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>3a</td>
<td>50% TFA, reflux</td>
<td>5a (60)</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3a</td>
<td>4 equiv of BF(_3)-OEt(_2), rt</td>
<td>5a (55)</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>3b</td>
<td>50% TFA, reflux</td>
<td>5b (50)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>3b</td>
<td>4 equiv of BF(_3)-OEt(_2), reflux</td>
<td>5b (71)</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>3b</td>
<td>2 equiv of BF(_3)-OEt(_2), reflux, 3 h</td>
<td>5b (69)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield. \(^b\) Addition by syringe pump over 12 h.

Dilute solutions of trifluoroacetic acid (TFA) in CH\(_2\)Cl\(_2\) were sufficiently acidic to produce iminium ions from acetal 1. Reactions conducted at reflux under high dilution (entry 1) gave the best yields. Similar reaction in acidic MeOH gave 4a albeit in lower yield. The major competing pathway is presumed to be polymerization.

Contrasting results were observed with the benzimidazolone substrate. Subjecting \( 2 \) to the same reaction conditions used for \( 1 \) (1% TFA in CH\(_2\)Cl\(_2\)) gave only recovered starting material. Increased acid concentration (25–50% v/v TFA in CH\(_2\)Cl\(_2\)) successfully produced benzomacrocycle 5a (Table 1, entry 4). Higher acid concentration may be required to shift the equilibrium toward the corresponding N-acyl iminium ion. Remarkably, slow addition of reactants was not necessary in this case: direct mixing of reactants provided dithiamacrocycles 5 in good yields (entries 4 and 6). Since high concentrations of TFA are not practical for larger scale reactions, we investigated the coupling using Lewis acids. Boron trifluoride etherate (2–4 equiv) was effective at reflux or under ambient conditions and gave similar yields in all cases studied (entries 4 vs 5; 6 vs 7).

The macrocycles 4 and 5 are \( N,S \)-acetals and therefore susceptible to acid-catalyzed elimination in a manner analogous to that of the \( N,O \)-acetals used as starting materials. For syringe pump addition of reagents to be most effective, it is desirable for reagents to be rapidly and irreversibly converted to the corresponding macrocycle. To shed light on possible equilibration, crossover experiments were performed. Equimolar amounts of 4b and scavenging dithiol 3a were reacted under typical reaction conditions (Scheme 1). In the presence of TFA at reflux, crossover was detected by TLC within 30 min, confirmed by GC-MS and \(^1\)H NMR analysis. After 12 h, a 42% combined yield (NMR yield, vs internal standard) of 4b and crossover product 4a was obtained in an ca. 1:1 ratio. The loss of mass is presumed to be a result of competing polymerization. Polymerization under the equilibrating conditions may account for the lower yields in the imidazolidinone cyclizations and suggests that high dilution conditions should be maintained throughout the addition. The equilibrium represented in eq 3 was also achieved in the presence of boron trifluoride etherate catalyst at room temperature. Contrasting results were observed in the benzimidazolones. Crossover was not evident for 5b with 3a using BF\(_3\)-OEt\(_2\). The acid stability of 5b helps explain the consistently higher yields in the benzimidazolone series.

The structures of thiamacrocycles 5 were unambiguously assigned by X-ray crystallography. Racemic crystals of 5b (mp 223.5–225 °C) were obtained by slow evaporation of

---

(5) Heterophanes are [2.2]-cyclophanes that contain at least one heterocyclic ring system. In cyclophane nomenclature, \([m,n]\) refer to the number of atoms in the bridge between the two ring systems. The \( m,n \) descriptor is omitted because it is not appropriate with regard to the heterocyclic nucleus; the sites of substitution on the heterocycle are denoted in parentheses, see: Paudler, W. W.; Bezoari, M. D. Synthesis and Properties of Heterophanes. In Cyclophanes, Vol. 2; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983.


---

Scheme 1. Crossover Experiment
a dichloromethane solution in a pentane atmosphere.\textsuperscript{11} The ORTEP drawing is shown in Figure 1. The two aromatic
rings are roughly parallel with an angle between the mean planes of $\theta = 9.9(2)^\circ$. The aromatic rings are separated by a mean distance of 3.320(3) Å.

Cyclophanes that contain a sulfur in the bridge are useful precursors to [2.2]cyclophanes D (Scheme 2, eq 4). In the

Figure 1. ORTEP drawing of cyclophane 5b. Thermal ellipsoids are drawn at 50\% probability.

\begin{center}
\textbf{Scheme 2.} Sulfur Extrusion and Prepared [2.2]Imidazolidophanes 6, 7a, and 7b
\end{center}

(9) Imidazolidine and benzimidazolone dichlorides were also coupled with benzene-1,4-dimethanethiol 3a under basic conditions ($\text{C}_6\text{H}_5\text{CO}_2\text{H}$) by syringe pump addition (12 h) to give the products C (eq 1) in 26\% and 20\% yields, respectively. The combination $\text{NaOH}/\text{EtOH}$ gave ethoxy substitution product in the benzimidazolone series in contrast with successful literature macrocyclizations employing benzylic dihalides (ref 6). This latter observation led us to consider the source of the presumably greater reactivity in benzimidazolone dichlorides. Preparation of dihalides: (a) Petersen, H.; Reuther, W. Liebigs Ann. Chem. 1972, 766, 58. (b) Zinner, H.; Spangenberg, B. Chem. Ber. 1958, 91, 1432.


(11) X-ray intensity data were collected on a MAC Science DPH-2020K imaging-plate diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å) using a colorless crystal with the dimensions $0.2 \times 0.2 \times 0.2$ mm$^3$. Intensity data were integrated with the DENZO program and scaled with the SCALEPACK program. The crystal structure was solved by direct methods with SHELXS and by the full-matrix least-squares method using SHELXL. All of the non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were located from difference Fourier ($F_s - F_r$) maps and refined isotropically, each with its own isotropic temperature parameter. Crystal data for 5b: $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, FW = 156.49 g/mol, monoclinic, space group $\text{C}2/c$ (No. 15), unit cell dimensions (Å): $a = 27.300(6); b = 9.3010(19); c = 17.5844(4)$, $\beta = 92.37(7)$, $\gamma = 94.50(6)$, $V = 3431.5(1.2)$ Å$^3$, $D_c$ = 1.372 g/cm$^3$, $\rho_{\text{calc}}$ = 0.0748 for all 2798 independent reflections, 356 parameters. GOF($F^2$) = 3.96\% for 3398 reflections with $R_s > 0$ and $R_w(F^2) = 0.1085$ for all 3606 independent reflections, 298 parameters, GOF($F^2$) = 1.051. The racemate 5b was separated by HPLC using a chiral column (Chiralcel OD-H, 4.6 mm × 30 cm, 10\% IPA-hex, rt 10.01, 32.65 min). When pure enantiomer was collected and reinjected, there was no evidence of racemization. Heating 5b in pyridine (reflux, 1 h), did not result in racemization. Further studies of conformational issues are ongoing.


(14) (a) Bruhin, J.; Jenny, W. Tetrahedron Lett. 1973, 1215. (b) Bockelheide, V.; Reingold, I. D.; Tuttle, M. J. Chem. Soc., Chem. Commun. 1973, 406. (15) X-ray diffraction data were collected on a Bruker 1K CCD diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation using a colorless crystal with the dimensions $0.25 \times 0.25 \times 0.25$ mm$^3$. Intensity data were integrated with SHELXS and refined by full matrix least-squares method with SHELXL. All the non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were located from difference Fourier ($F_s - F_r$) maps and refined isotropically, each with its own isotropic temperature parameter. Crystal data for 5b: $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, FW = 156.49 g/mol, monoclinic, space group $\text{C}2/c$ (No. 15), unit cell dimensions (Å): $a = 27.300(6); b = 9.3010(19); c = 17.5844(4)$, $\beta = 92.37(7)$, $\gamma = 94.50(6)$, $V = 3431.5(1.2)$ Å$^3$, $D_c$ = 1.372 g/cm$^3$, $\rho_{\text{calc}}$ = 0.0748 for all 2798 independent reflections, 356 parameters. GOF($F^2$) = 3.96\% for 3398 reflections with $R_s > 0$ and $R_w(F^2) = 0.1085$ for all 3606 independent reflections, 298 parameters, GOF($F^2$) = 1.051. The racemate 5b was separated by HPLC using a chiral column (Chiralcel OD-H, 4.6 mm × 30 cm, 10\% IPA-hex, rt 10.01, 32.65 min). When pure enantiomer was collected and reinjected, there was no evidence of racemization. Heating 5b in pyridine (reflux, 1 h), did not result in racemization. Further studies of conformational issues are ongoing.


(15) X-ray diffraction data were collected on a Bruker 1K CCD diffractometer with Mo Kα ($\lambda = 0.71073$ Å) radiation using a colorless crystal with the dimensions $0.25 \times 0.25 \times 0.25$ mm$^3$. Intensity data were integrated with SHELXS and refined by full matrix least-squares method with SHELXL. All the non-hydrogen atoms were refined anisotropically. Positions of hydrogen atoms were located from difference Fourier ($F_s - F_r$) maps and refined isotropically, each with its own isotropic temperature parameter. Crystal data for 5b: $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, FW = 156.49 g/mol, monoclinic, space group $\text{C}2/c$ (No. 15), unit cell dimensions (Å): $a = 27.300(6); b = 9.3010(19); c = 17.5844(4)$, $\beta = 92.37(7)$, $\gamma = 94.50(6)$, $V = 3431.5(1.2)$ Å$^3$, $D_c$ = 1.372 g/cm$^3$, $\rho_{\text{calc}}$ = 0.0748 for all 2798 independent reflections, 356 parameters. GOF($F^2$) = 3.96\% for 3398 reflections with $R_s > 0$ and $R_w(F^2) = 0.1085$ for all 3606 independent reflections, 298 parameters, GOF($F^2$) = 1.051. The racemate 5b was separated by HPLC using a chiral column (Chiralcel OD-H, 4.6 mm × 30 cm, 10\% IPA-hex, rt 10.01, 32.65 min). When pure enantiomer was collected and reinjected, there was no evidence of racemization. Heating 5b in pyridine (reflux, 1 h), did not result in racemization. Further studies of conformational issues are ongoing.
bond distortions. The angle strain enforced by the ethano bridges is manifest in the substituent distortion angle, the smallest angle made with the plane of the aromatic ring to which the substituent is attached. For instance, C-15 is distorted 15.8(2)° from the ideal coplanar arrangement with the benzimidazolone plane. The distortion angle of C-15 and C-14 is unequal; C-14 is distorted by 19.1(2)° due to transannular van der Waals repulsion of the C-12 methyl group with the benzimidazolone ring.

The effect of structural distortion was also evident in the spectroscopic properties of the cyclophanes. In particular, the carbon-13 chemical shift of the urea carbonyl carbon was affected. A summary of the urea carbonyl 13C data is shown in Table 2. In the imidazolidinone series, compression of

<table>
<thead>
<tr>
<th>entry</th>
<th>dithiacyclophane C</th>
<th>[2.2]cyclophane D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a, 154.3</td>
<td>6, 162.2</td>
</tr>
<tr>
<td>2</td>
<td>5a, 149.5</td>
<td>7a, 158.1</td>
</tr>
<tr>
<td>3</td>
<td>5b, 150.2</td>
<td>7b, 157.9</td>
</tr>
</tbody>
</table>

* Comparison: for 1, 13C(CO) = 159.8 ppm; 2, 13C(CO) = 154.5 ppm.

4a to the corresponding [2.2]heterophane 6 results in a downfield shift of 7.9 ppm (entry 1). Similar changes were seen in the benzimidazolone series, 5a to 7a (entry 2) and 5b to 7b (entry 3). These results are interpreted in terms of an anisotropy effect of the adjacent benzene ring and structural distortion of the urea from planarity caused by the rigidity of the [2.2]heterophane macrocycle.

In conclusion, a novel double N-acyl iminium ion cyclization has been used to prepare new cyclophanes that contain the imidazolidinone and benzimidazolone ring system. Photochemical extrusion of the bridging sulfur atoms to prepare the corresponding [2.2]imidazolophane was successful. The reactions and catalytic properties of these novel heterophanes and their analogues are currently being explored in our lab.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund (33298G1) and SUNY-Buffalo for support of this work. We also thank Professor Huw Davies for lending us photochemical equipment and Professor Philip Coppens for helpful discussions regarding the crystal structures.

Supporting Information Available: Detailed experimental procedures and characterization data for 4a, 5a, 5b, 6, 7a, and 7b. This information is available free of charge via the Internet at http://pubs.acs.org.

(16) [2.2]Paracyclophane is estimated to have 31 kcal/mol ring strain. Cram, D. J.; Cram, J. M. Acc. Chem. Res. 1971, 4, 204.
(17) For the parent [2.2]paracyclophane, the distortion angle is reported to be $\theta = 12^\circ$. See ref 16.