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

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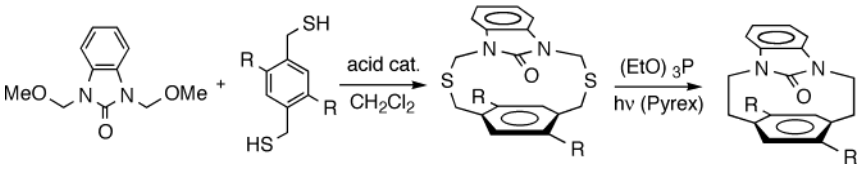
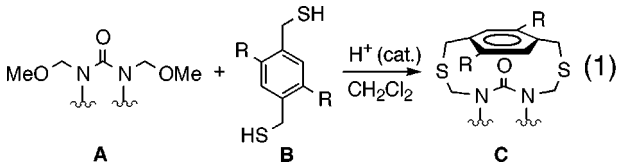
ABSTRACT



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.[1] Other recent applications include template-directed synthesis,[2] anion binding,[3] and catalysis.[4] In the [2.2]-cyclophanes, there are no examples that contain an imidazole or imidazolone ring. In the known cases of [2.2]heterophanes,[5] 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*-acyl iminium ion-type macrocyclization (eq 1).



The conventional synthesis of hydrocarbon-derived dithiacyclophanes utilizes nucleophilic displacement of organic dihalides, e.g., α,α′-dibromo-*p*-xylene, using bisthiol nucleophiles.[6] When conducted under high dilution conditions, this coupling method has proven successful for the synthesis of dithiacyclophanes;[1] however some cyclophanes are produced in moderate or low yields by this method.[7]

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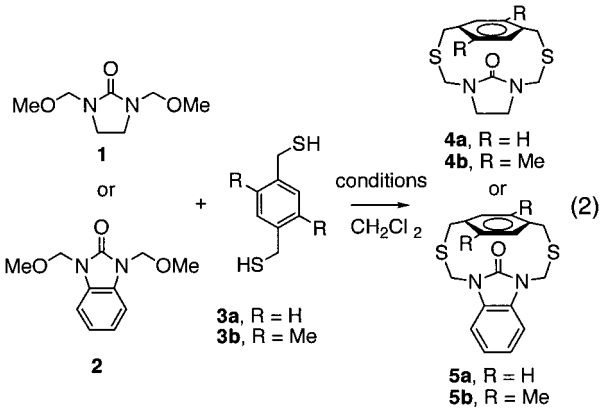
The acetal **A** can produce a highly electrophilic *N*-acyl iminium ion[8] under acidic conditions. Prompted by this knowledge, acidic reaction conditions were investigated using *N*,*O*-acetals rather than the corresponding dihalides, which are typically used in the base-catalyzed version of the macrocyclization.[9] Given the propensity of *N*,*O*-acetals to undergo acid-catalyzed transacetalization and that thiols[10] tolerate a variety of Brønsted and Lewis acidic conditions, we attempted to prepare macrocycles **4** and **5** using CF_3-COOH or $BF_3{\cdot}OEt_2$ catalysis in CH_2Cl_2 solvent (eq 2). The results for the macrocyclization are presented in Table 1.

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



entry	acetal	dithiol	conditions	product (yield, %)[a]
1	**1**	**3a**	1% TFA, reflux (slow add'n)[b]	**4a** (40)
2	**1**	**3a**	1% H_2SO_4, MeOH rt (slow add'n)[b]	**4a** (27)
3	**2**	**3a**	50% TFA, reflux (slow add'n)[b]	**5a** (43)
4	**2**	**3a**	50% TFA, reflux	**5a** (60)
5	**2**	**3a**	4 equiv of $BF_3{\cdot}OEt_2$, rt	**5a** (55)
6	**2**	**3b**	50% TFA, reflux	**5b** (50)
7	**2**	**3b**	4 equiv of $BF_3{\cdot}OEt_2$, rt	**5b** (71)
8	**2**	**3b**	2 equiv of $BF_3{\cdot}OEt_2$, reflux, 3 h	**5b** (69)

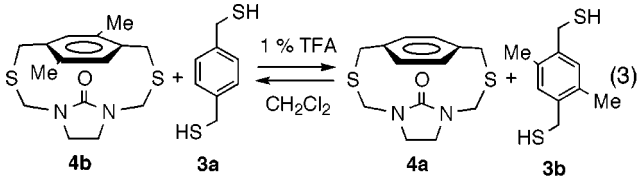
[a] Isolated yield. [b] Addition by syringe pump over 12 h.

Dilute solutions of trifluoroacetic acid (TFA) in CH_2Cl_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_2Cl_2) gave only recovered starting material. Increased acid concentration (25−50% v/v TFA in CH_2Cl_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

Scheme 1. Crossover Experiment



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 $BF_3{\cdot}OEt_2$. 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 *para* 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.

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(8) The use of *N*-acyl iminium ions in synthesis: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

a dichloromethane solution in a pentane atmosphere.[11] The ORTEP drawing is shown in Figure 1. The two aromatic

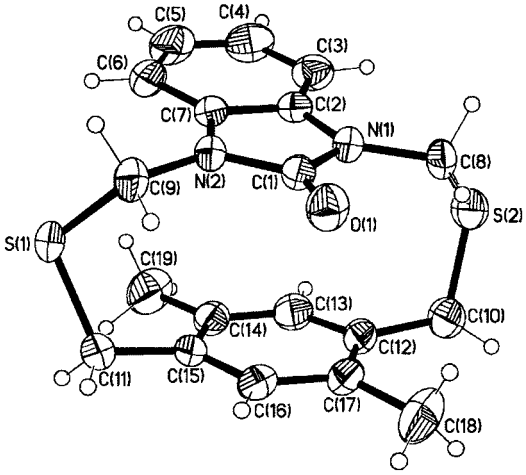
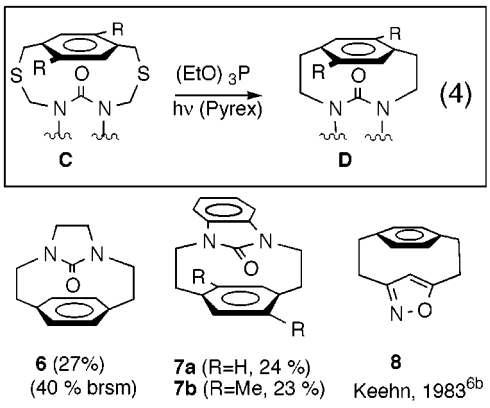


Figure 1. ORTEP drawing of cyclophane **5b**. Thermal elipsoids are drawn at 50% probability.

rings are roughly parallel with an angle between the mean planes of $\theta = 9.9(2)°$. 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

Scheme 2. Sulfur Extrusion and Prepared [2.2]Imidazolophanes **6**, **7a**, and **7b**



past, [2.2]heterophanes have been constructed by two principal strategies. Cram synthesized furanophane by thermal co-1,6-elimination, "cross-breeding", of 5-methylfurfuryltrimethylammonium hydroxide and *p*-xylyltrimethylammonium hydroxide.[12] The resulting furanophane could be subsequently converted into pyrrole[13] and thiophene analogues. A second approach used for a variety of hydrocarbon cyclophanes employs cyclization under high dilution followed by sulfur atom extrusion ($h\nu$, $(EtO)_3P$).[14] In the present case, cyclophane **6** was synthesized by photochemical extrusion in 27% isolated yield (40% based on recovered starting material, unoptimized) from sulfur macrocycle **4a**. The [2.2]benzimidazolocyclophanes were prepared in a two-step sequence from acetal **2** and *p*-xylenedithiols **3** (eq 2 above) without purification of the intermediate dithiamacrocycles **5**. In this way, crystalline benzimidazolones **7a** and **7b** were isolated in 24 and 23% yields after flash chromatography. This sequence compares favorably with the literature preparation of related [2.2](2,4)isoxazolocyclophane **8** which was prepared in 52% (cyclization) and 7% yield (sulfur extrusion).[6b]

A crystal of **7b** (mp 183−187 °C) was obtained from a saturated solution in dichloromethane and subjected to single-crystal X-ray structure analysis.[15] The ORTEP drawing is shown in Figure 2. In this compound, the centers of the aromatic planes are separated by a mean distance of 3.030-(3) Å, compressed relative to the dithiaphane **5b**. The new cyclophane **7b** is highly strained[16] and shows characteristic

(9) Imidazolidinone and benzimidazolone dichlorides were also coupled with benzene-1,4-dimethanethiol **3a** under basic conditions (Cs_2CO_3) by syringe pump addition (12 h) to give the products **C** (eq 1) in 26% and 20% yields, respectively. The combination NaOH/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.

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(11) X-ray intensity data were collected on a MAC Science DIP-2020K imaging plate diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å) using a colorless crystal with the dimension $0.2 \times 0.2 \times 0.2$ 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 ($F_o - F_c$) maps and refined isotropically, each with its own isotropic temperature parameter. Crystal data for **5b**: $C_{19}H_{20}N_2OS_2$, FW = 356.49 g/mol, monoclinic, space group *C*2/*c* (No. 15), unit cell dimensions (Å) $a = 27.300(6)$; $b = 9.3010(19)$; $c = 17.584(4)$, $\beta = 129.37°$, $V = 3451.5(1.2)$ Å^3, $Z = 8$, $T = 298(2)$ K, $D_c = 1.372$ g/cm^3, $2\theta_{max} = 54.94°$, $R(F) = 3.96\%$ for 3398 reflections with $F_o > 4\sigma(F_o)$ and $Rw(F^2) = 0.1085$ for all 3606 independent reflections, 298 parameters, GOF(F^2) = 1.051. The racemate **5b** was separated by HPLC using a chiral column (Chiracel 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.

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(14) (a) Bruhin, J.; Jenny, W. *Tetrahedron Lett.* **1973**, 1215. (b) Boekelheide, 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 of $0.25 \times 0.25 \times 0.25$ mm^3. Intensity data were integrated with SAINT program. The crystal structure was solved by direct methods 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 ($F_o - F_c$) maps and refined isotropically, each with its own isotropic temperature parameter. Crystal data for **7b**: $C_{19}H_{20}N_2O$, $M = 292.37$, orthorhombic, chiral space group $P2_12_12_1$ (No. 19), $a = 7.5911(7)$ Å, $b = 13.9115(11)$ Å, $c = 14.3428(10)$ Å, $V = 1514.7(2)$ Å^3, $Z = 4$, $T = 298(2)$ K, $D_c = 1.282$ g·cm^{-3}, $2\theta_{max} = 55.22°$, $R(F) = 3.58\%$ for 2274 reflections with $F_o > 4\sigma(F_o)$ and $Rw(F^2) = 0.0748$ for all 2798 independent reflections, 280 parameters. GOF(F^2) = 0.954. Absolute configuration could not be determined due to a lack of heavy atoms.

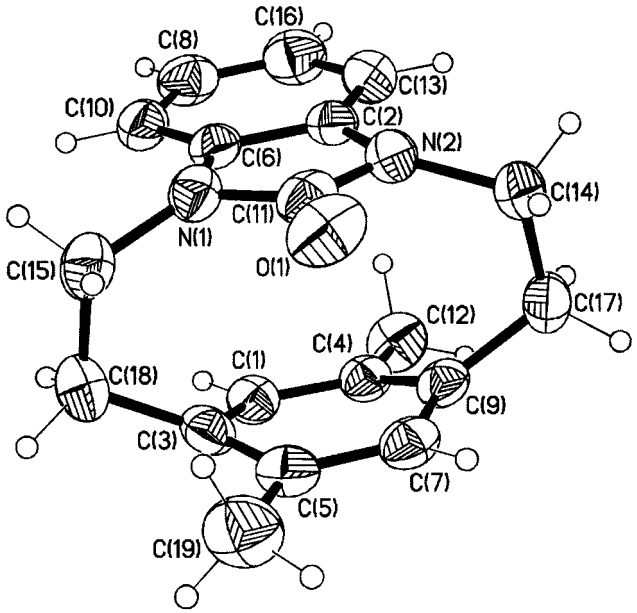

Figure 2. ORTEP drawing of [2.2]benzimidazolophane **7b**. Thermal elipsoids are drawn at 50% probability.

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.[17] 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 ^{13}C data is shown in Table 2. In the imidazolidinone series, compression of **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.

Table 2. Urea Carbonyl ^{13}C Chemical Shifts ($CDCl_3$, ppm)[a]

entry	dithiacyclophane **C**	[2.2]cyclophane **D**
1	**4a**, 154.3	**6**, 162.2
2	**5a**, 149.5	**7a**, 158.1
3	**5b**, 150.2	**7b**, 157.9

[a] Comparison: for **1**, $^{13}C(CO) = 159.8$ ppm; **2**, $^{13}C(CO) = 154.5$ ppm.

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.

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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.

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(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 $\theta = 12°$. See ref 16.