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A novel entry into a new class of cyclophane derivatives: synthesis of (±)-[2.2]paracyclophane-4-thiol[†]

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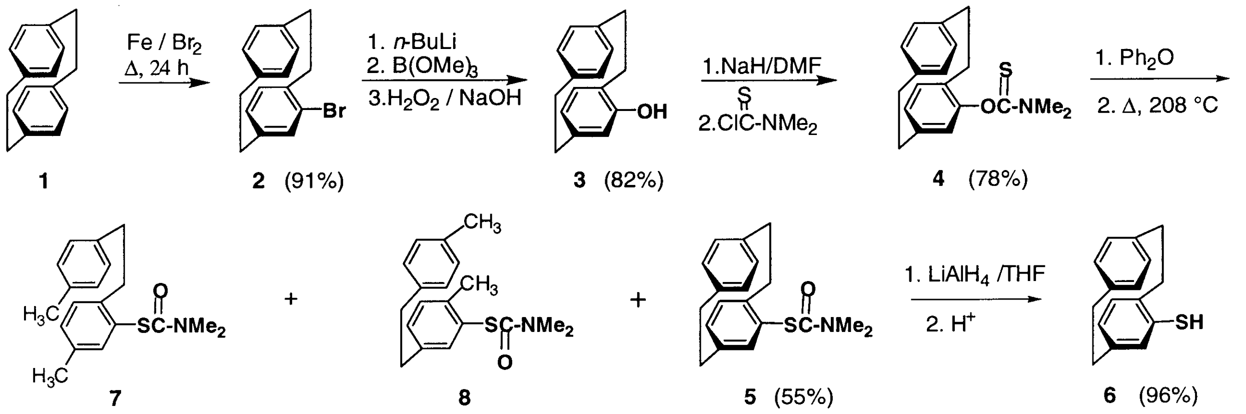
Abstract—Two syntheses of (±)-[2.2]paracyclophane-4-thiol have been accomplished in two and five steps, with overall yields of 46 and 31%, respectively, from [2.2]paracyclophane. The strategy involves two key reactions: (a) a lithium aluminium hydride reduction of the disulphide of [2.2]paracyclophane and (b) the use of a Newman–Kwart reaction for the conversion of [2.2]paracyclophane-4-ol to [2.2]paracyclophane-4-thiol. © 2001 Elsevier Science Ltd. All rights reserved.

The first rational synthesis of [2.2]paracyclophane (PCP) was described a half century ago by Cram and Steinberg.[1] One of us (H.H.) has been involved in [2.2]paracyclophane chemistry for the past thirty years and has utilised [2.2]paracyclophane for probing theories of bonding, ring strain and π electron interactions.[2] Two important developments during the past ten years are (a) the synthesis of fluoro derivatives of [2.2]paracyclophane[3] and their possible use in polymer industry, and (b) the use of monosubstituted [2.2]paracyclophanes as planar chiral templates or auxiliaries.[4] The latter development has rejuvenated the interest in the synthesis of [2.2]paracyclophane derivatives. This has resulted in numerous methods for their enantioselective synthesis. These cyclophane enantiomers are stable towards light, oxidation, base, acid and thermal stress up to 180°C, and are finding widespread applications as ligands in asymmetric catalysis, particularly as hydroxy and P–P based ligands with phosphorus attached to the [2.2]paracyclophane.[5] However, ligands are also known with sulphur attached to each benzene ring of PCP.[6] The related enantiomeri-



Scheme 1. Synthesis of thiol **6** using the Newman–Kwart reaction.

Keywords: [2.2]paracyclophane; Newman–Kwart reaction.

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[†] This paper is dedicated to Professors Fritz Bickelhaupt and Willem H. De Wolf.

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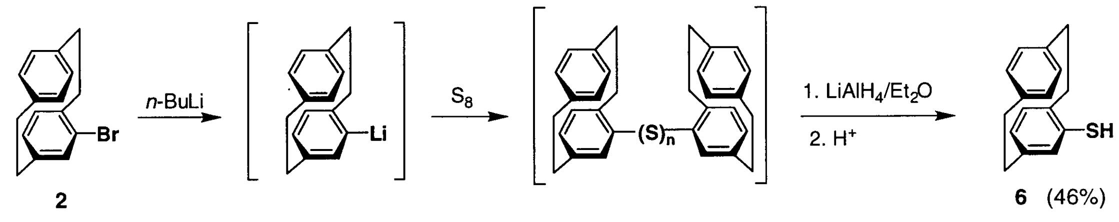
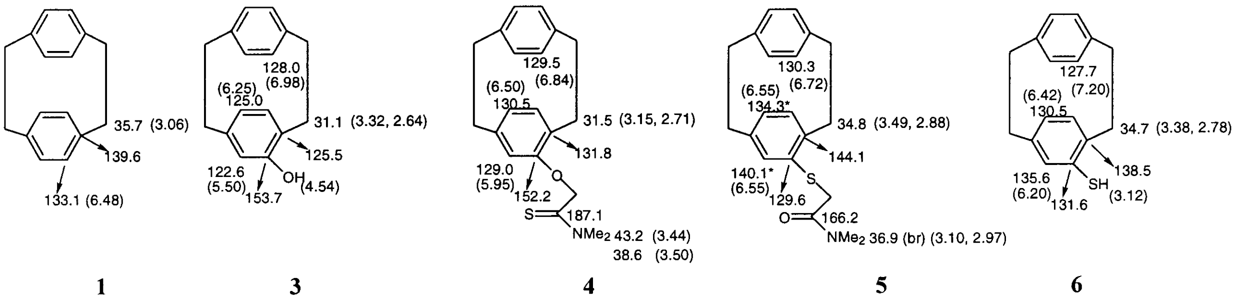


Scheme 2. Alternate synthesis of [2.2]paracyclophane-4-thiol.



Scheme 3. Important ^{1}H and ^{13}C NMR chemical shifts of **6** compared to **1** and **3**–**5**.

cally pure monothio-[2.2]paracyclophane has not yet been reported. We reasoned that such a thio derivative could be converted to a thioacetal in order to study an asymmetric reaction of its anion with α,β-unsaturated ketones, a reaction that needs to be explored since it will open new synthetic pathways to natural products. In the first phase of our program we developed the highly expeditious synthesis of this so far elusive (±)-[2.2]paracyclophane-4-thiol by two routes.

The overall synthetic plan is depicted in Scheme 1. A key requirement in the synthesis is the conversion of *O*-aryl dimethylthiocarbamate **4** to *S*-aryl dimethylthiocarbamate **5** by the use of the Newman–Kwart reaction. Bromination of [2.2]paracyclophane **1** using essentially the method of Cram and Day[7] gave 91% of a mixture containing mainly monobromide **2** (86% by ^{13}C NMR), mp 203–204°C. This monobromide was lithiated in ether with 2.2 equiv. of *n*-BuLi and the resultant organolithium intermediate was treated with trimethyl borate. Subsequent hydrolysis of the borate ester with hydrogen peroxide and sodium hydroxide gave phenol **3**, mp 224–225°C (82%).[8] Treatment of **3** with sodium hydride in DMF generated the sodium salt and subsequent addition of dimethylthiocarbamoyl chloride gave the desired *O*-aryl dimethylthiocarbamate **4** in 78% yield, mp 214–215°C.[9] Difficulties were encountered in the conversion of the *O*-aryl dimethylthiocarbamate using literature procedures.[10] The best reaction conditions found consisted of heating **4** exactly at 208°C under N_2 in diphenyl ether for 50 hours, which gave a mixture from which the desired **5** could be obtained in 55% yield after chromatography on silica gel. This was not unexpected since large alkyl groups at an *ortho* position slow the reaction and in general cause a lower yield.[11] Also, [2.2]paracyclophane is unstable above 200°C over a long period of time.[12] This is clearly shown by the isolation of a mixture of two ring opening products **7** and **8** in the ratio of 1:2. Several attempts to improve the yield failed. Reduction of **5** with lithium aluminium hydride in THF at 65°C gave (±)-[2.2]paracyclophane-4-thiol (**6**) (90%), mp 140–141°C.

The second and shorter synthesis (Scheme 2) consists of the treatment of the organolithium salt intermediate with sublimed sulphur (S_8). The crude product thus obtained was not characterised but reduced with lithium aluminium hydride in ether to give [2.2]paracyclophane-4-thiol **6** (46%), identical in all respects to the compound prepared earlier in Scheme 1 (mixed mp, NMR, IR).

We could fully assign the ^{13}C and ^{1}H NMR spectra of **6** including the bridge proton multiplets. Important chemical shifts of **6** are given in Scheme 3 and are compared with those of its precursors **1** and **3**–**5**. Fig. 1 shows the experimental and simulated ^{1}H NMR spectra at 400 MHz of the aromatic protons of **6**.

Fig. 2 shows the molecular structure of intermediate **4** as obtained from an X-ray diffraction measurement.[13]

Conclusion. This communication describes the synthesis and properties of (±)-[2.2]paracyclophane-4-thiol. The resolution using chiral reagents has not yet been successful. However, previously we, Cipicani and his colleagues have obtained enantiomerically pure phenol **3**.[14,15] Its conversion to the thiol using the Newman–Kwart reaction is in progress and will be reported at a later date.

Acknowledgements

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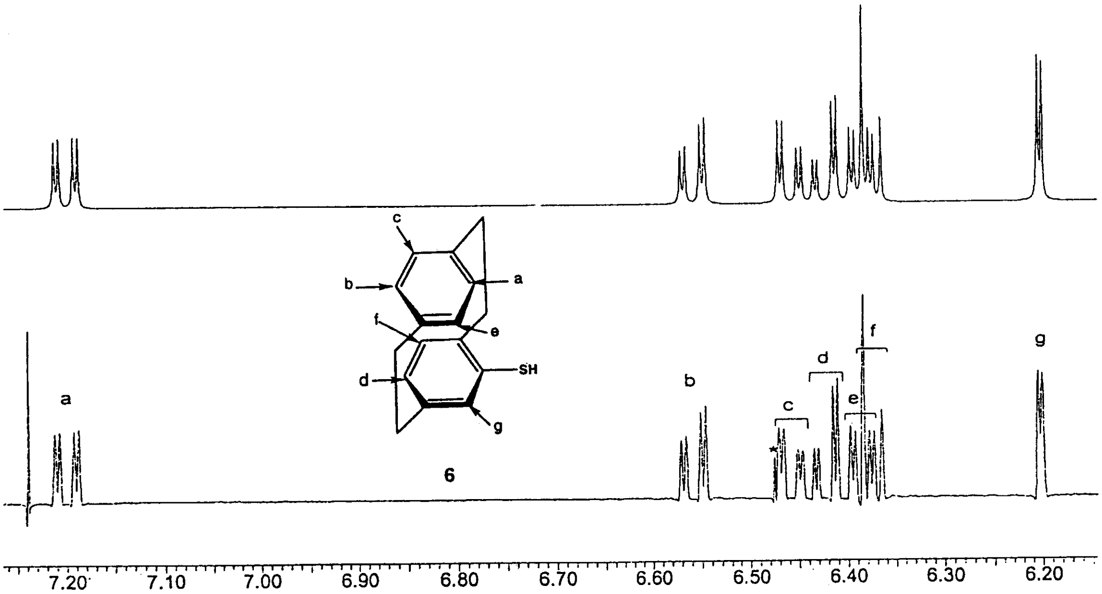

Figure 1. Aromatic region of the 400 MHz ^{1}H NMR spectrum of **6** in $CDCl_3$; experimental (bottom), simulated (top).

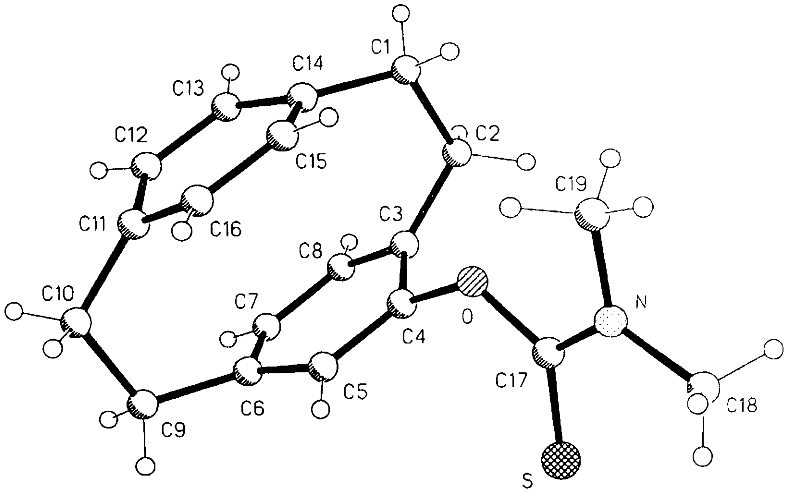

Figure 2.

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13. Crystal structure determination of compound **4**; monoclinic, $P2_1/c$, $a = 17.858(3)$, $b = 7.6615(12)$, $c = 11.6150(17)$ Å, $\beta = 92.869(4)°$, $V = 1587.1$ Å^3, $Z = 4$, $T = -130°C$. 16263 reflections were recorded on a Bruker SMART 1000 CCD diffractometer. The structure was refined on F^2 (program SHELXL-97, G.M. Sheldrick, University of Göttingen) to $wR_2 = 0.0149$, $R_1 = 0.0544$ for 201 parameters, 201 restraints and 2708 unique reflections. Full details have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC-151374 and may be obtained free of charge from deposit@ccdc.cam.ac.uk.
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