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An Unusual Thioketal Formation: Attempted Synthesis of 2,3-Dibromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene

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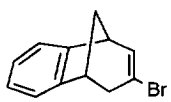
Abstract : Treatment of **8** with 2 equiv. of NBS gave tetra bromide **9** which was converted to the corresponding unsaturated ketone **7**. Reaction of **7** with 1,2-ethanedithiol produced the unusual thioketal **14** besides normal ketalization product **13**. Reduction of **13** with Raney nickel resulted in the formation of hydrocarbon **17**, instead of the expected dibromide **4**.

Introduction

The synthesis and isolation or trapping of highly strained molecules, such as cyclic allenes and alkynes, has been an area of extensive research during the past thirty years[1]. In a previous paper[2], we reported that the highly strained allene **2** is the intermediate in the base-catalyzed elimination of HBr from **1** to give the 1,3-diphenylbenzoisofuran (DBI) trapping products. However, an alternative mechanism for the formation of allene-like adducts can be envisioned that requires the dehydrobromination of **1** to yield the bicyclic alkyne **3** which undergoes cycloaddition with DBI. The base-promoted isomerization of the double bonds in alkyne-like adducts would then give the observed allene-like adducts. In order to distinguish between these two possible mechanisms[3], the alkyne **3** must be generated by alternate procedures and subsequently trapped with DBI. For this purpose we were interested for the synthesis of **4**. In the present work we report our results on the synthesis of **4** and observation of an unprecedented thioketal formation.



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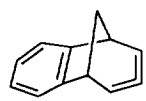

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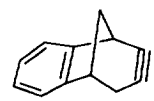

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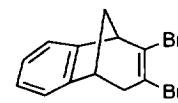

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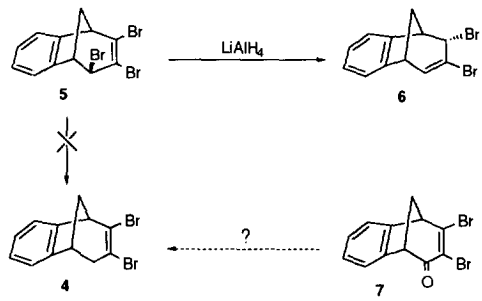
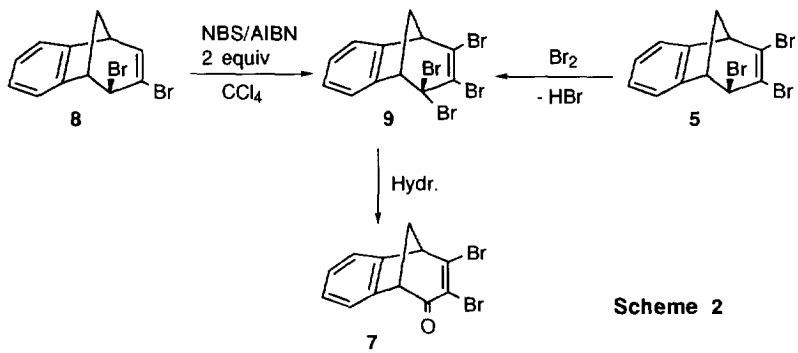
Results and Discussion

Our first attempt for the synthesis of dibromo compound **4** was $LiAlH_4$ reduction of **5** which resulted in the formation of endo-dibromide **6** via a S_N2' mechanism[4] (Scheme 1). As a second approach, we have planned to generate the desired compound **4** by reduction of the carbonyl group of the unsaturated ketone **7** (Scheme 1). Ketone **7** was prepared as shown in Scheme 2.

Tetra bromide **9**, the starting material for the synthesis of **7**, was prepared by bromination of tribromide **5** followed by spontaneous dehydrobromination as reported in the literature[5]. Silver ion catalyzed hydrolysis of **9** afforded smoothly the ketone **7**. Spectroscopic data of **7** were consistent with the structural assignment.

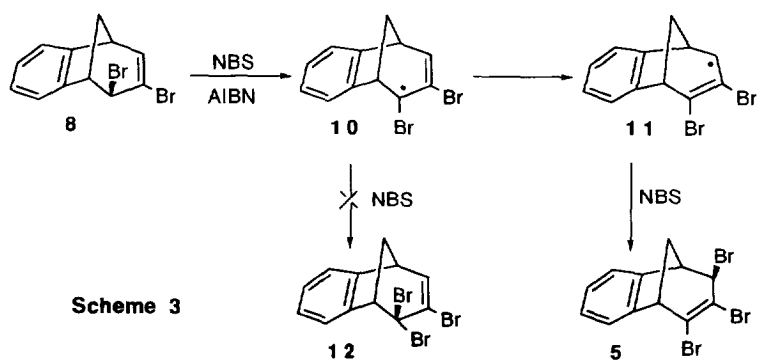


Scheme 1



Scheme 2

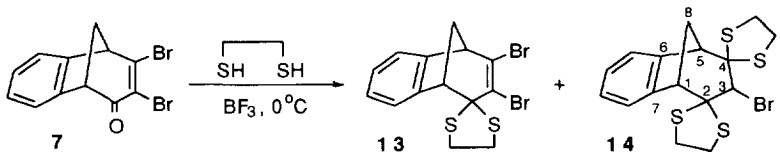
Independently, we have developed a short and convenient method for the synthesis of tetra bromide **9**. Treatment of **8**[6] with 2 equiv. of N-bromosuccinimide (NBS) and a catalytic quantity of AIBN in CCl_4 gave tetra bromide **9** in high yield (75%). We have also shown that the tribromide **5** is formed by the reaction of **8** with 1 equiv. of NBS under the same reaction conditions. The unusual conversion of **8** to **5** where a vinylic bromination takes place can be reasonably explained by the following mechanism involving the allylic radicals **10** and **11.**



Scheme 3

We assume that the primarily formed allylic radical **10** completely rearranges to **11** before recombination of allylic radical **11** and NBS to give tribromide **5**. Allylic bromination product **12** was not detected in this reaction even in any trace. Recently, we have observed a similar allylic rearrangement in this system and confirmed this observation by deuterium labeling studies[4]. More recently, Paquette et al.[7] have observed similar results in cyclooctadiene systems.

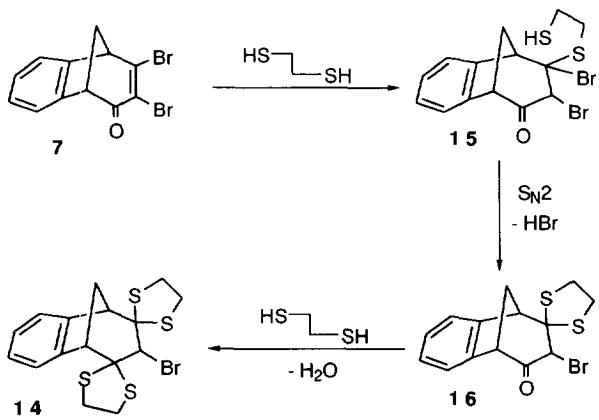
Reaction of the unsaturated ketone **7** with ethanedithiol in the presence of boron trifluoride etherate gave two products, the thioketals **13** and **14** in a yield of 66, and 17%, respectively (Scheme 4).



7 13 14

Scheme 4

Thioketal **13** is the expected product in this reaction which is formed directly by ketalization of the unsaturated ketone **7**. The ^{1}H- and ^{13}C-NMR spectra of **13** were completely in agreement with the proposed structure. Dithioketal **14** has also been characterized by means of spectral data. The mass spectra of **14** (M^{+} = 416/418) and analysis of the ^{1}H- and ^{13}-NMR spectra indicated the existence of one bromine atom in **14** . On the other hand, a nine-line ^{13}C-NMR spectrum supports strongly the proposed symmetrical structure. However, the configuration of bromine atom (exo or endo) at C_3 atom in **14** could not be determined on the basis of NMR spectral data. The formation of **14** during this thioketalization reaction is unexpected but in view of the formation mechanism is interesting. For the unusual formation of **14** we propose following reaction mechanism (Scheme 5).



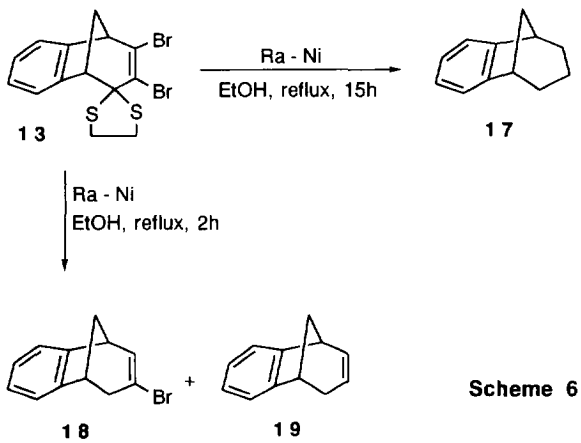
7 15 16 14

Scheme 5

According to this mechanism, firstly, a Michael-type addition takes place between ethanedithiol and the α, β-unsaturated ketone **7** to yield **15**. Subsequently, an intramolecular nucleophilic displacement of bromine

by sulphur in **15** gives **16** through a S_N2 reaction. Normal ketalization of **16** in the final step affords dithioketal **14**. This reaction can be applied for the synthesis of protected 1-3-dicarbonyl compounds.

Finally, treatment of thioketal **13** with Raney nickel in absolute ethanol at the reflux temperature for 15 h gave the completely reduced hydrocarbon **17** as the sole product instead of the expected dibromide **4** (Scheme 6). Spectral data of **17** matched with those reported in the literature[8].



13 **17** **18** **19**

Scheme 6

The desulphurization of **13** for 2 h under the same reaction conditions formed a mixture of **18**[6], and **19**[9] (Scheme 6). All efforts to carry out the reaction under the milder reaction conditions did not allow to isolate the dibromo compound **4**. The synthesis of dibromide **4** was not succeeded by the desulphurization of **13**. Further works on the synthesis of **4** are in progress.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Solvents were concentrated at reduced pressure. Infrared spectra were obtained from KBr pellets or from solution in 0.1 mm cells on a regular instrument. The ^1H- and ^{13}C-NMR spectra were recorded on 60-, 200-, and 400- MHz spectrometers. Mass spectra were recorded at 70 eV as m/z. All column chromatography was performed on silica gel (60-mesh, Merck).

2,3,4,4-Tetrabromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene 9. A mixture of **8** (1.32 g, 4.2 mmol), N-bromosuccinimide (1.54 g, 8.6 mmol), 2,2-azobisisobutyronitrile (5 mg), and CCl_4 (30 mL) was heated at reflux for 12 h, cooled, and filtered to remove succinimide. After the solvent was removed, the residue was purified on a short silica gel column eluted with petroleum ether to give 1.48 g (75%) of **9** as a colorless crystalline solid, mp 115-116 °C from $CHCl_3$/n-hexane (1:3). The NMR spectrum was identical to that reported[5].

2,3,4-Tribromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene 5. The reaction was carried out as described above by using 1 equiv. of NBS. The reaction mixture was heated at reflux for 2.5 h, and the tribromide **5**[4] was obtained as the sole product in a yield of 87%.

3,4-Dibromo-6,7-benzobicyclo[3.2.1]octa-3,6-dien-2-one 7. To a solution of **9** (0.75 g, 1.58 mmol) in CH_2Cl_2 (20 mL) was added $AgNO_3$ (0.54 g, 3.19 mmol), silica gel (5 g), and water (2 mL). The mixture was stirred at room temperature for 24 h, filtered and the filter cake washed thoroughly with CH_2Cl_2. After removing of the solvent, the oily residue (0.52 g) was crystallized from CCl_4 to give unsaturated ketone **7** (0.33 g, 63%); colorless crystals : mp 104-105 °C ; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.42 (m, 2H, aromatic H), 7.20 (m, 2H, aromatic H), 4.22 (d, J=4.0 Hz, 1H), 4.12 (d, J=4.0 Hz, 1H), 2.90 (d, J=10.8 Hz, 1H), 2.69 (dt, J=10.8, 4.0 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 187.80, 153.64, 145.81, 139.80, 127.89, 127.86, 125.76, 123.34, 121.15, 56.36, 56.04, 48.91 ; IR (KBr, cm^{-1}) 3060, 2970, 2860, 1695, 1560, 1455, 1220, 1120, 1030, 770. Anal. Calcd for $C_{12}H_8Br_2O$: C, 43.94 ; H, 2.46; Found : C, 43.89; H, 2.55.

Reaction of 3,4-Dibromo-6,7-benzobicyclo[3.2.1]octa-3,6-dien-2-one 7 with 1,2-Ethanedithiol. 0.32 mL of boron trifluoride etherate (0.37 g, 2.62 mmol) was slowly added to a solution of the pure unsaturated ketone **7** (0.72 g, 2.19 mmol) and 0.66 mL of 1,2-ethanedithiol (0.76 g, 12.2 mmol) in 5 mL of dry ether cooled in an ice bath. The resulting reaction mixture was stirred at 0 °C for 10 min and then heated with stirring at 40-50 °C for 25 min. After the reaction mixture was cooled to room temperature, 15 mL of methanol was added, and a yellow precipitate appeared immediately. Stirring was continued at rt for 5 min. The supernatant was decanted, and the residue was washed with MeOH, recrystallized from $CHCl_3$/MeOH and obtained 140 mg (17%) of dithioketal **14** as slightly yellow needles crystals : dec. 150 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 2H, aromatic protons), 7.25 (m, 2H, aromatic protons), 4.35 (s, 1H, H-3), 3.65 (br s, 2H, bridgehead protons), 3.59 (m, 2H, S-CH_2), 3.39-3.49 (m, 4H, S-CH_2), 3.31 (m, 2H, S-CH_2), 2.51 (br s, 2H, bridge methylenic protons, H-8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.56 (C_6,C_7), 127.95, 124.64, 76.89 (C_2,C_4), 75.09 (C_3), 56.94 (C_1,C_5), 44.09 (C_8), 42.63 (CH_2S), 39.42 (CH_2S); IR (KBr, cm^{-1}) 3020, 2950, 2920, 1470, 1460, 1430, 1420, 1285, 1275, 1190, 1010, 835, 765, 685, 600, 520 ; MS (m/z, %) 416/418 (M^+, 10), 337 (M^+-Br, 100). Anal. Calcd for $C_{16}H_{17}BrS_4$: C, 46.03; H, 4.10; S, 30.72; Found : C, 46.22; H, 4.17; S, 30.68.

The supernatant obtained by decantation was evaporated. The yellowish oily residue (0.7 g) was chromatographed over silica gel (30 g). Elution with petroleum ether gave 540 mg (66%) of thioketal **13** : colorless crystals (from CH_2Cl_2-pentane), mp 132-134 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.48 (m, 1H, aromatic H), 7.21 (m, 3H, aromatic H), 3.84 (d, J=4.5 Hz, 1H, bridgehead proton), 3.76 (d, J=4.1 Hz, 1H, bridgehead proton), 3.34-3.61 (m, 4H, -SCH_2-CH_2S), 2.55 (d, J=11.2 Hz, 1H), 2.47 (dt, J=11.2, 4.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 149.88, 141.41, 131.42, 128.12, 127.68, 127.47, 121.98, 77.84, 57.55, 53.21, 45.61, 42.95, 41.51. IR (KBr, cm^{-1}) 3070, 3020, 2960, 2915, 1570, 1470, 1450, 1420, 1300, 1275, 1095, 1025, 765, 750, 680, 620, 535, 525. Anal. Calcd for $C_{14}H_{12}Br_2S_2$: C, 41.60; H, 2.99; S, 15.86; Found : C, 41.22; H, 2.84; S, 15.95.

Reduction of 2,2-(1,2-Ethylenedithio)-3,4-Dibromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene 13 with Raney nickel. A mixture containing 4,2 g of Raney nickel and 0.6 g (1.48 mmol) of the thioketal **13** in 40 mL of absolute ethanol was heated at reflux temperature for 15 h. After the reaction mixture was cooled to room temperature, the insoluble materials were separated by filtration. The filtrate was evaporated,

and the residue was chromatographed over silica gel, eluting with petroleum ether to give 65 mg (28%) of hydrocarbon **17** as a colorless liquid. The NMR spectrum was identical to that reported[8].

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