Addition of dibromocarbene to cyclobutene: characterisation and mechanism of formation of the products

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Cyclobutene reacted with dibromocarbene in solution to give 1,5-dibromocyclopent-1-ene (**9**), 1,2,6,6-tetrabromobicyclo[3.1.0]hexane (**10**), and 1,2,3,6-tetrabromocyclohex-1-ene (**11**), in a ratio of 1:4:8, respectively. Compounds **10** and **11** were found to be formed from a second carbene addition and rearrangement under the given reaction conditions.

Keywords: carbene, carbene addition, cyclopropane, cyclobutene

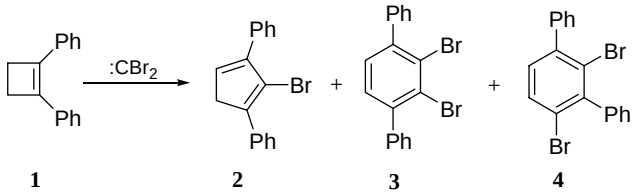
Carbenes are versatile intermediates that undergo insertion, rearrangement and facile addition reactions and their importance for synthetic chemists cannot be overestimated.[1] The most common and thoroughly investigated reaction of carbenes is their addition to carbon-carbon double bonds. Although much literature concerning dihalocarbene reactions with open chain and cyclic alkenes larger than four-membered rings exists, only a few studies with small-ring alkenes have been reported.[2,3] Brinker[3] and coworkers have reported that when 1,2-diphenylcyclobutene (**1**) was treated with dibromocarbene, the reaction gave derivatives of cyclopentadiene and of benzene **2–4** (Scheme 1).

Very recently Lewis and coworkers[4] have reported that the reactions of difluorocarbene with 1,2-diphenylcyclobutene (**1**) gave 1,3-difluoro-2,4-diphenylbenzene (**5**) in one step by ring expansion. This represents a unique way to make this class of compounds, which are very difficult to obtain, starting from benzene. Recently, we published the synthesis of *gem*-bromofluorocyclopropane **7** starting from the olefin **6** and its conversion to the corresponding strained cyclic allene.[5]

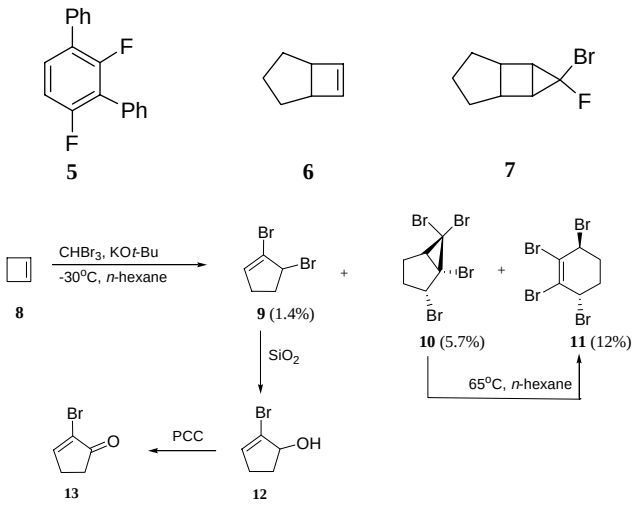
As far as we know, there is no detailed report concerning the addition of dihalocarbenes to unsubstituted small ring carbocycles such as cyclobutene. Herein, we wish to disclose our results for the addition of dibromocarbene to cyclobutene (**8**).

In a search of a convenient source of cyclobutene, we have found that cyclobutyl tosylate can provide cyclobutene (**8**) free of its isomeric impurities in good yields.[6] The addition of dibromocarbene generated from $CHBr_3$ and KO*t*-Bu to cyclobutene (**8**) at –30°C produced adducts **9**, **10**, and **11** in a ratio of 1:4:8, respectively (Scheme 2).

The spectroscopic data for 1,5-dibromocyclopentene **9** were in good agreement with those previously reported.[7] The attempt to purify compound **9** indicated that it hydrolyses to a small extent to the corresponding alcohol **12** during the column chromatography. The structure of alcohol **12** was also proved chemically by oxidation to the known ketone **13**.[7] The structure of 1,2,6,6-tetrabromobicyclo[3.1.0]hexane (**10**) was elucidated on the basis of NMR and MS spectroscopic data. The GC–MS spectrum showed the presence of four bromine atoms with an M^+ signal corresponding to 393. The ^{1}H NMR spectrum of **10** revealed five sets of proton signals; a doublet of doublets centered at 4.66 ppm, a doublet of doublets of doublets at 2.03 ppm and three sets of multiplets at 2.39, 2.66 and 2.84 ppm. The exact configuration of the bromine atom at the C-2 carbon atom could not be determined. However, when the cyclopropane adduct **10** was heated in *n*-hexane at 65°C, it rearranged smoothly to the 1,2,3,6-tetrabromocyclohex-1-ene (**11**), thus clearly indicating an isomeric relationship between these two compounds. It was also noted that this rearrangement of **10** to **11** takes place upon standing at room temperature for a few days. The isomeric tetrabromide **11** showed a broad doublet (J = 2.3 Hz) at 4.77 ppm and two quasi doublets (J = 10.7 Hz) centered at 2.52 and 2.07 ppm, respectively. The three-line[13] C-NMR spectrum clearly shows the symmetry in the molecule. The *trans*-configuration of the bromine atoms at the C-3 and C-6 carbon atoms was determined unambiguously by X-ray crystallographic analysis (Fig. 1).[8]



Scheme 1



Scheme 2

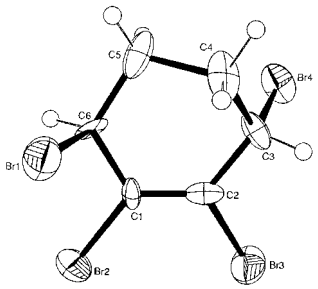


Fig. 1 The X-Ray crystal structure of 11.

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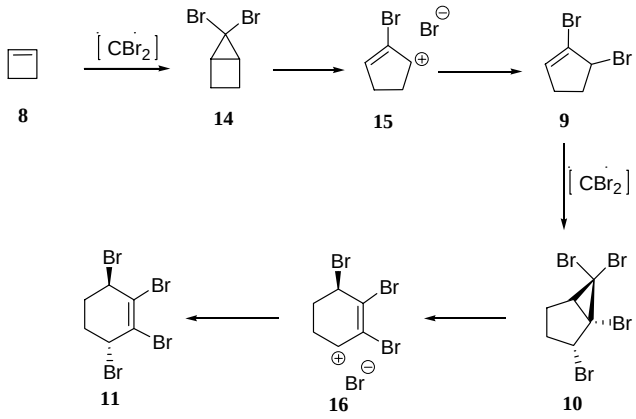
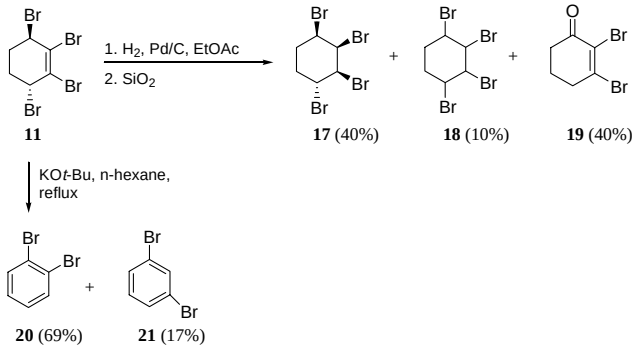
The mechanism for the formation of the products presumably involves the intermediacy of the strained 5, 5-dibromobicyclo[2.1.0]pentane (**14**). Electrocyclic ring opening reaction[9] of **14** produces first the cation **15** (Scheme 3). The dissociation of the bromide ion and the opening of the three membered-ring takes place at the same time. Capture of the bromide gives the dibromide **9**. Addition of a second mole of CBr_2 to the double bond in **9** forms the bicyclic addition product **10**.

The exclusive formation of the tetrabromide **11** upon heating of **10** indicates that the ring opening process is governed by the Woodward–Hoffman rules. The *trans*-configuration of the bromine atoms at C-3 and C-6 carbon atoms in **11** proves furthermore the *trans*-configuration of the bromine atom at C-2 and the cyclopropane ring in **10.** It is noteworthy that the second addition of the carbene to **9** is directed towards the sterically less-hindered face of the double bond which is in agreement with the stereochemistry of the tetrabromide **10.**

Moreover, catalytic hydrogenation of **11** in ethyl acetate followed by column chromatography on SiO_2 gave a mixture of two inseparable tetrabromides **17** and **18** (4:1), (the configuration of **18** is not known), besides the 2,3-dibromocyclohex-2-en-1-one (**19**). The mechanism of formation of **19** is currently under investigation. On the other hand, the HBr elimination from **11** gave a mixture of aromatic compounds of which spectral data were consistent with 1,2-dibromobenzene **20** and 1, 3- dibromobenzene **21**, respectively (Scheme 4).



Scheme 3



Scheme 4

Experimental

General: Melting points were determined on a Büchi model 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson model 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on 400 (100) MHz spectrometers. Mass spectra (electron impact) were recorded at 70 eV. Column chromatography was performed on silica gel (60-200 mesh) from Merck Company. TLC was carried out on Merck 0.2 mm silica gel 60 F254 analytical aluminum plates.

*Synthesis of cyclobutene **(8)** and dibromocarbene addition:* A solution of tosyloxycyclobutane[6] (6.78 g (30 mmol)) in dry DMSO (10 ml)was added dropwise over 10 min to a stirred mixture of KOt-Bu (8.4 g (75 mmol)) in dry DMSO (120 ml) at 80°C under the stream of nitrogen. After stirring and heating for 100 min the evolved cyclobutene **9** (b.p. 2°C) was carried in nitrogen into a trap containing a solution of $CHBr_3$ (3.9 g (15 mmol)) in *n*-hexane (100 ml) cooled to –80°C). Then the mixture was allowed to warm to –30° and KOt-Bu (1.7 g (14 mmol)) was added. The mixture was allowed to warm up to room temperature, washed with ice cold water and extracted with hexane (3×100 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with hexane as eluent until no more fractions were collected to give **9, 10**, and **11** in a ratio of 1:4:8 respectively. Finally, elution of the column material with 9:1 hexane-EtOAc gave the alcohol **12**.

The first fraction: *1,5-Dibromocyclopentene* **(9)**[7]**:** liq. 95 mg (1.4%); ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (bs, 1H), 4.81 (m, 1H), 2.49 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 124.0, 60.5, 35.8, 31.6.

The second fraction: *1,2,6,6-tetrabromo-bicyclo[3.1.0]hexane* **(10):** 670mg (5.7 %); ^1H NMR (400MHz, $CDCl_3$) δ 4.66 (dd, *J* =7.1, 2.0 Hz, 1H), 2.84 (m, 1H), 2.66 (m, 1H), 2.39 (m,2H), 2.03 (ddd, *J*=13.6, 8.9, 2.0 Hz, 1H). ^{13}C NMR (100 MHz $CDCl_3$) δ 56.8, 48.1, 38.4, 33.4, 28.6, 27.6. IR ($CHCl_3$, cm^{-1}) 2919, 2360, 2329, 1688, 1549, 1424, 1260, 1219, 1133, 1101, 1027, 913, 847, 775, 743, 691, 651, 607, 477. MS *m/z* 392/394/396/398/400 (M^+, 8%), 313/315/317/319 (M^+-HBr, 38%), 234/236/238 (M^+-2HBr, 82%), 155/157 (M^+–2HBr, -Br, 66%), 77 (100). Anal. Calcd for $C_6H_6Br_4$: C, 18.12; H, 1.52. Found: C, 18.08; H, 1.48.

148 (M^+, 23%), 133 (100), 115 (37), 115 (37), 105 (100), 91 (100), 77

The third fraction: *(3R(S),6R(S))-1,2,3,6-tetrabromocyclohex-1-ene* **(11):** White solid, m.p. 126-128 °C, 1.43g (12%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (bd, *J* = 2.3 Hz, 2H), 2.07 (quasi d, *J* = 10.7 Hz, 1H), 2.51 (quasi d, *J* = 10.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.4, 52.9, 29.3. IR ($CHCl_3$, cm^{-1}) 2956, 2921, 2851, 2353, 1594, 1462, 1431, 1378, 1303, 1202, 1152, 1111, 1046, 998, 952, 867, 785, 706, 647, 581, 510, 442. Anal. Calcd for $C_6H_6Br_4$: C, 18.12; H, 1.52. Found: C, 18.16; H, 1.46.

The fourth fraction: *2-Bromocyclopent-2-enol* **(12)**[7]**:** 180 mg (3.8%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (bs, 1H), 4.46 (m, 1H), 3.13 (bs, OH), 2.16 (m, 3H), 1.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 125.6, 79.3, 32.3 30.6. IR ($CHCl_3$, cm^{-1}) 3343, 3079, 2934, 2853, 2694, 1618, 1434, 1325, 1238, 1153, 1050, 986, 922, 901, 814, 772, 583, 432.

Hydrogenation of tetrabromide **11:** Into a 50 ml, two-necked, round-bottomed flask were placed Pd/C (10%) (10 mg) catalyst and of the tetrabromide **11** 100 mg (0.25 mmol) in AcOEt (20 ml). One of the necks was attached to hydrogen gas with a three-way stopcock, the other neck was capped with a rubber septum. The reactants were degassed and flushed with hydrogen gas, while stirring magnetically. After 4 h the solution was decanted from the catalyst, the solvent rotoevaporated and the residue chromatographed on silica gel with hexane-EtOAc (19:1) as eluent.

The first fraction consisted of a mixture of **17** and **18** (50 mg, 49%, in a ratio of 4:1). *(1R(S),2R(S),3S(R),4R(S))-1,2,3,4-tetrabromo-cyclohexan*e **17**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (bs, 1H), 4.34 (bs, 1H), 2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.3, 53.6, 26.6. IR ($CHCl_3$, cm^{-1}) 2958, 2955, 2854, 2088, 1639, 1461, 1434, 1378, 1305, 1278, 1203, 1116, 1051, 970, 914, 852, 773, 728, 686, 628, 530, 476.

18: ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (bs, 1H), 4.25 (bs, 1H), 2.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.0, 51.5, 28.7. IR ($CHCl_3$, cm^{-1}) 2955, 2850, 2095, 1650, 1451, 1443, 1370, 1296, 1260, 12001, 1126, 1043, 980, 912, 851, 776, 725, 680, 622, 538, 496. (The exact configuration of **18** was not determined).

As the second fraction, the enone **19** was isolated. *2, 3-Dibromocyclohex-2-en-1-one* **(19)** : 24 mg (40%). ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (t, *J* = 6.1 Hz, 2H), 2.48 (t, *J* = 6.5 Hz, 2H), 1.98 (qui., *J* = 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 149.1, 128.0, 38.9, 37.2, 22.8. Ms *m/z* 252/254/256 (M^+, 100%), 224/226/228 (M^+ –CO, 49%), 173/175 (M^+ –Br, 62%), 145/147 (M^+ –CO, –HBr, 70%), 117/119 (36%). (Anal. Calcd for $C_6H_6Br_2O$: C, 28.38; H, 2.38. Found: C, 28.23; H, 2.32

1,2-Dibromo (20) and 1,3-dibromobenzene **(21)** : A solution of **11** (100 mg (0.25 mmol)) and KOt-Bu (120 mg (1.07 mmol)) in THF

(30 ml) was refluxed for 1 h. After adding water, the mixture was extracted with hexane (3×50 ml) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed to give a mixture (51 mg, 86%) of **20** and **21** in a ratio of 4:1, whose spectral data was consistent with the literature.[10]

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