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Bromination of 1,2-Dimethylenecyclohexane: Temperature Effect on Product Distribution

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Highlights

- The bromination reactions of 1,2-dimethylcyclohexane were examined.
- The reaction temperatures and the amount of the bromine affected the product distributions.
- As the temperature increased, it caused a decrease in the amount of kinetically controlled product
- The rise in temperature led to an increase in radicalic addition products.
- Increasing the amount of bromine produced an increase in the amounts of radicalic addition products.

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Abstract

In this study the electrophilic addition of bromine to an exocyclic diene, 1,2 dimethylenecyclohexane, was investigated. The bromination of 1,2-dimethylenecyclohexane yielded 1,2-bis(bromomethyl)cyclohex-1-en at low temperature. Nevertheless, the bromination of 1,2-dimethylenecyclohexane at room temperature gave 1,4 addition product 1,2-bis(bromomethyl)cyclohex-1-en as a main product together with 1-bromo-1-(bromomethyl)-2-methylenecyclohexane and 3-bromo-1,2-bis(bromomethyl)cyclohex-1-ene. Similarly, high temperature bromination of 1,2-bismethylenecyclohexane gave the radical bromination products (3-bromo-1,2-bis(bromomethyl)cyclohex-1-ene and 3,6-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene) in addition to the 1,4 addition product. While the bromination of exocyclic diene at room temperature with excess bromine gave tetrabrominated product 1,2-dibromo-1,2-bis(bromomethyl)cyclohexane as a sole product, the bromination of exocyclic diene in high temperature with excess bromine resulted in a tetra brominated product 1,2-dibromo-1,2-bis(bromomethyl)cyclohexane and the three brominated product 3-bromo-1,2-bis(bromomethyl)cyclohex-1-ene together with the radicalic tetrabrominated product 3,6-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene as main products. However, the high temperature bromination of 1,4 brominated product with excess bromine provided only the radicalic brominated product 3-bromo-1,2-bis(bromomethyl)cyclohex-1-ene and 3,6-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene. Thus the functional agents which can be used as starting material in the synthesis of many compounds were synthesized, purified and characterized.

1. INTRODUCTION

Cyclic dienes such as 1,2-dimethylenecyclohexane (**1**) and 1,2-dimethylenecyclopentane (**2**) have attracted interest because their production of multicyclic adducts which are used as a starting material to synthesize of many natural products by using the Diels Alder reaction and electrophilic addition of their conjugated double bonds (Figure 1) [1-9].



Figure 1. 1,2-Dimethylenecyclohexane (**1**) and 1,2-dimethylenecyclopentane (**2**)

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Brominated compounds, which are used as intermediates in the synthesis of many compounds, have synthetic importance as a starting material. One of the well known reactions of unsaturated compounds is formally the addition of bromine to the carbon-carbon double bond [10,11]. The structure of the addition of the intermediates is related to the structure of the substrate and the reaction medium. As a matter of fact previous studies have shown that the temperature of the reaction has a dramatic effect on product distribution [12-16].

The intermediates, bridged bromonium ions, take part in the bromination reaction of non-conjugated olefins that produce anti-adducts. However, the bromination of unsaturated bicyclic systems gives way to the rearrangements of the molecular skeleton. For instance, the electrophilic addition of bromine to oxabenzonorbornadiene (**3**) causes the rearranged product formation of dibromoaldehyde **4** in high yield (Figure 2) [17].

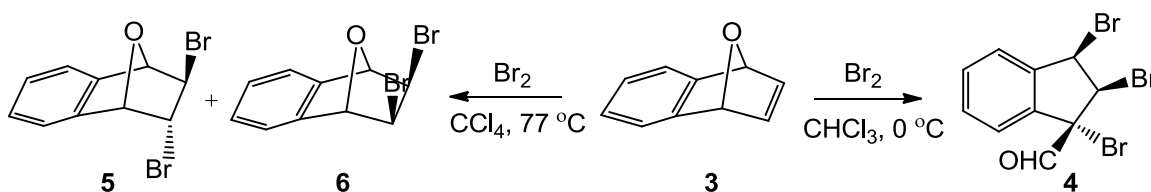


Figure 2. Bromination reactions of oxabenzonorbornadiene

If electrophilic addition is carried out on a compound having nonconjugated dienes, the product frequently obtained is a 1,2-addition. In the conjugated system, the 1,4-addition product is the most stable one as regards the thermodynamically controlled product, and it becomes dominant. Most of the times, when the reaction conditions exist, the 1,2-addition product turns into a mixture of 1,2- and 1,4- addition products which is full of 1,4- addition product [18].

Electrophilic additions of bromide to conjugated dienes usually contain allylic cations which have bromine as intermediates. Bromide found in the reaction medium can enter into a reaction with a nucleophilic from any of its positive centers to produce 1,2-addition and 1,4-addition products, in turn. The effect of temperature on product distribution is one of the most interesting properties of electrophilic addition reaction of conjugated dienes. When the reaction is carried out in different temperatures, usually the 1,2-addition product is present in higher amounts at lower temperatures while the more 1,4-addition product is formed at higher temperatures [18].

The bromination of bicyclic molecule **7** at different temperatures yielded interesting results. In contrast to acyclic systems in the low-temperature (0°C) bromination of **7**, the 1,2-adduct was more stable and formed in greater amounts than the 1,4-adduct as a thermodynamically controlled product (Figure 3). Since the 1,4-adduct increases the ring strain in the molecule, the exocyclic double bond formation with 1,2-addition is more stable and preferential [19].

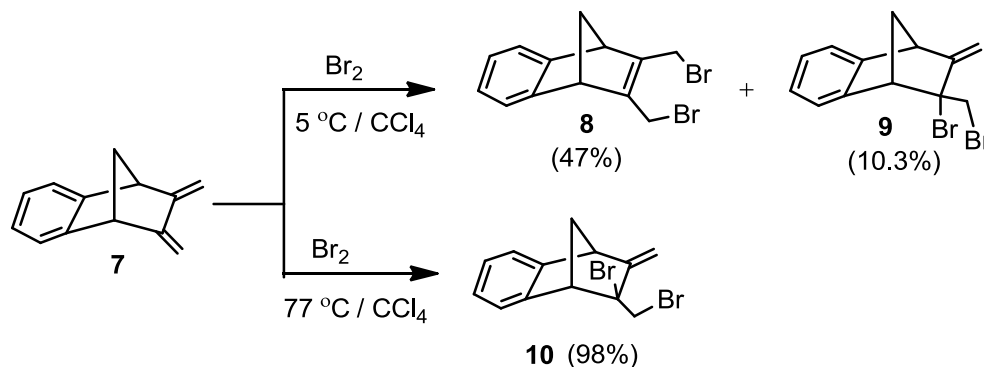


Figure 3. Products distributions of the bromination of exocyclicdiene **7** under the several reaction conditions

2. RESULTS AND DISCUSSIONS

First 1,2-dimethylenecyclohexane (**1**) was synthesized beginning from cis-1,2-cyclohexanedicarboxylic anhydride in three steps as reported in the literature (Figure 4) [5].

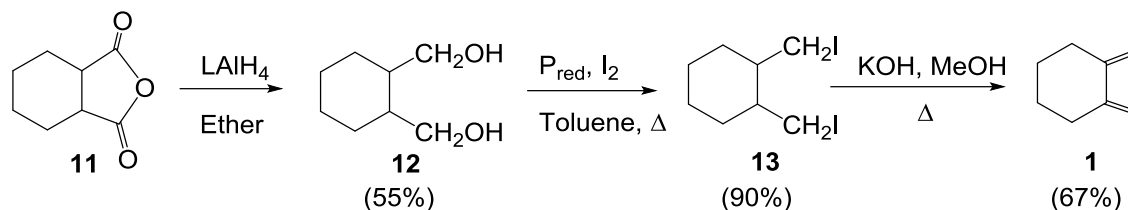


Figure 4. Synthesis of exocyclic diene (**1**)

It was determined by ^1H -NMR spectroscopy that the low temperature bromination of compound (**1**) in CCl_4 constituted mainly two products.

After the mixture was processed through a thin layer chromatography which is on silica gel, only product **14** was isolated at 50% yield (Figure 5). In the literature Schmidt and co-workers implied that while synthesizing disulfide, thioester and thiophene derivatives; 1,2-dimethylenecyclohexane reacted with bromide at room temperature gave **14**, a pale yellow and eye watering liquid [20].

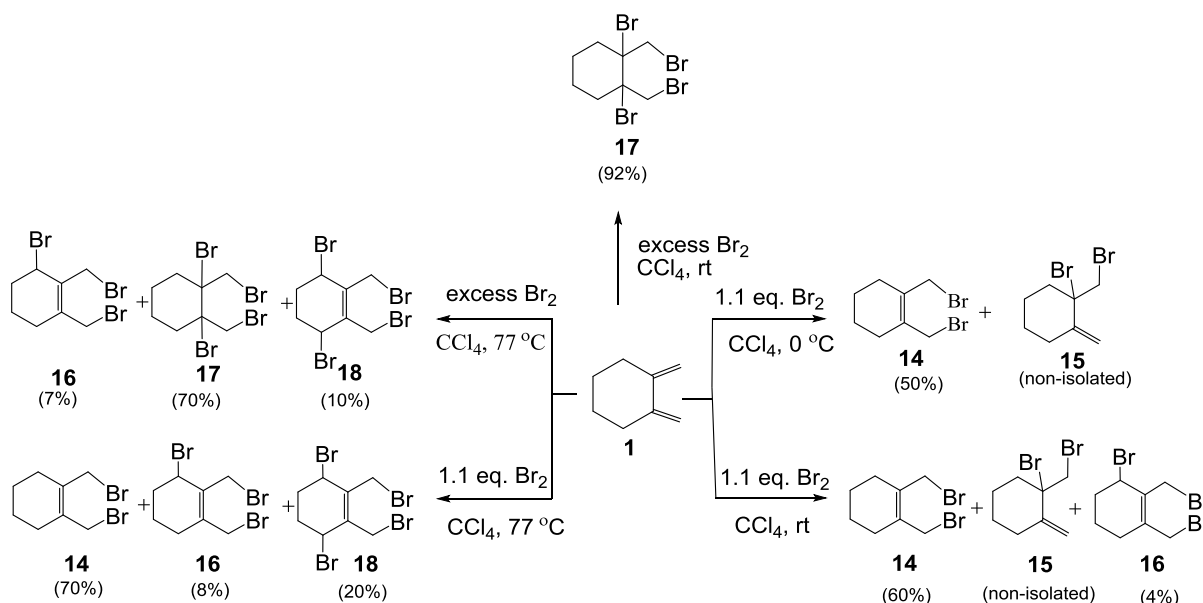


Figure 5. Bromination reactions of exocyclic diene **1** under different reaction conditions

The structure of product **14** was primarily identified with ^1H and ^{13}C HMR spectra. The ^1H NMR spectra show three signals: δ 4.00, 2.20, 1.70 ppm. The signal at δ 4.00 ppm is characteristic to methylene (CH_2Br) protons. In the ^{13}C HMR spectra, the signals at δ 134.3, 31.8, 28.5, 22.4 ppm cooperated with structure symmetry.

At room temperature the bromination of 1,2-dimethylenecyclohexane (**1**), a solution of bromine in carbon tetrachloride was added in one portion to a stirring solution of **1** in carbon tetrachloride. After the removal of the solvent at low temperature, the ^1H NMR spectra of the reaction mixture were taken. The analysis of the crude product by ^1H NMR spectroscopy produced those three compounds. After the mixture was processed through a thin layer chromatography which is on silica gel, two products which are product **14** and compound **16** were isolated at ratios 60 and 4, respectively (Figure 5).

The structure of compound **16** was elucidated by ^1H NMR and ^{13}C NMR spectra analysis. The 200 MHz

^1H NMR shows the presence of one vinylic proton at δ 5.00 and two AB systems between δ 4.20-3.80. The eight signals in the ^{13}C NMR spectrum are consistent with the asymmetry in the molecule.

Furthermore, the high temperature bromination of 1,2-dimethylenecyclohexane (**1**) was examined at 77 °C. The hot bromine solution which is in CCl_4 was poured directly into a refluxing solution of **1** in CCl_4 at 77 °C. The ^1H NMR analysis of reaction mixture showed that this solution was consisted of three products. After the crystallization and column chromatography, it was possible to separate three compounds, **14**, **16**, and **18** from each other. Compound **18**'s structure was characterized by ^1H and ^{13}C NMR spectrum data. The ^1H NMR spectra of compound **18** set forth an AB system and AA'XX' coupling pattern arises from methylene (CH_2Br) and ring methylene protons. A ^{13}C NMR spectrum of (**18**) is highly symmetrical with regard to the symmetry in the molecule. Particularly, at δ 51.4, 48.8, 28.0, 27.9 ppm the four-line ^{13}C NMR spectrum of **18** is completely in harmony with **18**.

Furthermore, the bromination of **1** with excess bromine produced only tetra bromine **17** in 92% isolated yield at room temperature. The structure of **17** was determined by ^1H NMR and ^{13}C NMR spectroscopy. The ^1H NMR spectra of **17** exhibit AB system arising from the bromomethylene group (BrCH_2Br) which clearly indicates the addition of four bromine atoms to molecule **1** (Figure 5).

In order to carry out the high temperature bromination reaction of **1** with excess bromine; a hot solution of excess bromine in CCl_4 was added to a refluxing solution of **1** in CCl_4 .

The analysis of the crude product showed that the 1,4- addition product was not formed but tetra bromide **17** and radical bromination product **16**, **18** and a small amount of unidentified aromatic compound were produced. The compounds were purified with column chromatography on silica gel (Figure 6).

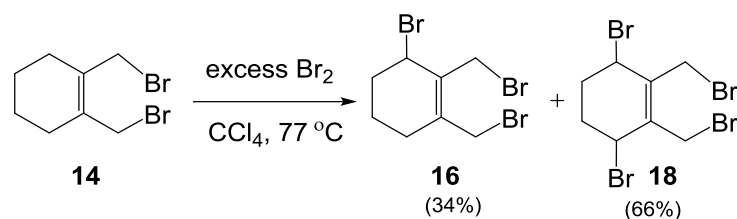


Figure 6. Bromination of 1,2-bis(bromomethyl)cyclohex-1-ene

3. EXPERIMENTAL

3.1. General

Melting points are not corrected. Infrared spectra were obtained from films on an NaCl plate for liquids and from a solution in 0.1 mm cell or KBr pellets for solids on a regular instrument. Nuclear Magnetic Resonance (^1H and ^{13}C) spectra were recorded on 400 (100) MHz spectrometers. Elemental analysis was determined on a Leco CHNS-932 instrument (Ataturk University/Erzurum). Column chromatographic separations were performed on silica gel (60-mesh, Merck). Thin Layer Chromatography was performed by using Merck 0.2 mm silica gel 60 F254 analytical aluminum plates.

3.2. Synthesis

3.2.1. Bromination of 1,2-Dimethylenecyclohexane (**1**) with 1 Equivalent Bromine at 0 °C

To a magnetically stirred solution of **1** (108 mg, 1.10^{-3} mol) in 1 ml of CCl_4 was added drop wise a solution of bromine (160 mg, 1.10^{-3} mol) in 1 ml CCl_4 at 0 °C. After the completion of the addition the resulting solution was stirred for 5 min. The solvent was evaporated. Product 1,2-bis(bromomethyl)cyclohex-1-en (**14**) was isolated by TLC eluting with hexane (R_f 0.65) and crystallized from MeOH (50% yield, 134 mg, colorless crystals melting at room temperature). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{Br}_2$: C, 35.85; H, 4.51. Found: C, 35.89; H, 4.48.

For (**14**);

^1H NMR (CDCl_3) δ : 4.00 (s, 4H); 2.20 (m, 4H); 1.70 (m, 4H) ppm. ^{13}C NMR (CDCl_3) δ : 134.3, 31.8, 28.5, 22.4 ppm. ν_{max} (liquid film): 2861, 2841, 2826, 1645, 1612, 1459, 1426, 1208, 617, 578 cm^{-1} .

3.2.2. Bromination of 1,2-Dimethylenecyclohexane (1) with 1 Equivalent Bromine at Room Temperature

To a magnetically stirred solution of **1** (200 mg $1.85 \cdot 10^{-3}$ mol) in 3 mL CCl_4 was added drop wise to the solution of bromine (270 mg, $1.68 \cdot 10^{-3}$ mol) in 1 mL CCl_4 at room temperature. After the completion of the addition the resulting solution was stirred for 5 min. The solvent was evaporated. The mixture was performed with TLC by eluting with hexane and two products were purified. The first line was the 1,4-addition product **14** with 60% yield. The second line was product 3-bromo-1,2-bis(bromomethyl)cyclohex-1-ene (**16**) as a liquid (4% isolated yield, 20 mg). Anal. Calcd for $\text{C}_8\text{H}_{11}\text{Br}_3$: C, 27.70; H, 3.20. Found: C, 27.75; H, 3.19.

For **16**;

^1H NMR (CDCl_3) δ 5.00 (1H, bs), 4.20 (1H, d, A part of AB system $J=11.0$ Hz), 4.10 (1H, d, B part of AB system $J=11.0$ Hz), 4.10 (1H, d, A part of AB system $J=10.5$ Hz), 3.80 (1H, d B part of AB system $J=10.5$ Hz), 2.45 (1H, dd, $J=12.0$, 5.1 Hz), 2.35 (2H, m), 1.91 (3H, m), 1.76 (1H, m) ppm. ^{13}C NMR (CDCl_3) δ : 138.2, 134.3, 50.6, 32.4, 30.4, 28.8, 28.5, 17.7 ppm. ν_{max} (liquid film): 2959, 2924, 2852, 1461, 1428, 1338, 1188, 1061, 974, 899, 825, 709, 622, 532, 492.

3.2.3. Bromination of 1,2-Dimethylenecyclohexane (1) with 1.1 Equivalent Bromine at 77 °C

To a magnetically stirred solution of **1** (310 mg $2.87 \cdot 10^{-3}$ mol) in 5 mL CCl_4 was added drop wise to the solution of bromine (459 mg, $2.87 \cdot 10^{-3}$ mol) in 5 mL CCl_4 at 77 °C. After the completion of the addition the resulting solution was stirred for 5 min. The solvent was evaporated. ^1H -NMR spectra indicated that the main product was **14** 70% and minor products were **18** (20%) and **16** (8%) conversion. To separate the products hexane added in the reaction mixture the 3,6-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene **18** was crystallized as a white color (12% yield, 184 mg, m.p. 128-130 °C). The remaining part after crystallation was separated with hexane on the silica gel column. It was observed that **14** in fraction 3-6 and **16** material in fraction 7-8. Anal. Calcd for $\text{C}_8\text{H}_{10}\text{Br}_4$: C, 22.57; H, 2.37. Found: C, 22.59; H, 2.27.

For **18**;

^1H NMR (CDCl_3) δ 5.05 (2H, CH-Br, bs), 4.13 (2H, CH_2 -Br, d, A part of AB system $J=11.0$ Hz), 4.05 (2H, CH_2 -Br, d, B part of AB system $J=11.0$ Hz), 2.42 (2H, m), 2.20 (2H, m), ppm. ^{13}C NMR (CDCl_3) δ : 136.4, 48.8, 28.1, 28.0 ppm. ν_{max} (nujol): 2980, 2890, 1410, 1290, 710, 580.

3.2.4. Bromination of 1,2-Dimethylenecyclohexane (1) with Excess Bromine at Room Temperature

To a magnetically stirred solution of exocyclic dien **1** (250 mg $2.31 \cdot 10^{-3}$ mol) in 5 mL CCl_4 was added drop wise 5 eqv. of bromine (1.84 g $11.55 \cdot 10^{-3}$ mol) solution in 1 mL CCl_4 at room temperature. After the completion of the addition the reaction mixture was stirred additional for 5 min. The solvent was removed under reduced pressure. Tetra bromine added product 1,2-dibromo-1,2-bis(bromomethyl)cyclohexane (**17**) was isolated as a sole product. Recrystallized from pentane, as colorless crystals (92% yield, 1.14 g, m.p. 92-94 °C). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{Br}_4$: C, 22.46; H, 2.83. Found: C, 22.51; H, 2.78.

^1H NMR (CDCl_3) δ 4.35 (2H, methylenic CH_2 -Br, d, A part of AB system $J=11.5$ Hz), 4.15 (2H, methylenic CH_2 -Br, d, B part of AB system $J=11.5$ Hz), 2.45 (2H, CH_2 , d, $J=15$ Hz), 2.15 (2H, CH_2 , m), 1.78 (2H, CH_2 , m), ppm. ^{13}C NMR (CDCl_3) δ : 75.3, 43.9, 36.6, 22.1 ppm. ν_{max} (KBr): 2940, 2921, 2870, 1439, 1363, 1252, 1150, 932, 861, 638, 520.

3.2.5. Bromination of 1,2-Dimethylenecyclohexane (1) with Excess Bromine at 77 °C

To a refluxing solutions of 1,2-dimethylenecyclohexane (**1**) (310 mg $2.7 \cdot 10^{-3}$ mol) in 5 mL of CCl_4 was added a hot solution of 5 eqv. bromine (2.2 g $1.38 \cdot 10^{-2}$ mol) in 2 mL CCl_4 . The resulting mixture was kept at the reflux temperature for 5 min. Then the solvent was removed under vacuum. The crude mass was chromatographed on silica gel eluting with 2% CH_2Cl_2 -hexane. The compounds **16**, **17** and **18**, were

isolated in 7% (70 mg), 70% (858 mg) and 10% (122 mg) yields, respectively.

3.2.6. Bromination of 1,2-Bis-(bromomethyl)cyclohexene (**14**) with Excess Bromine at 77 °C

To a refluxing solution of 1,2-bis-(bromomethyl)cyclohexene (**14**) (60 mg 0,224 mmol) in 3 mL of CCl₄ was added to the hot solution of 5 eqv. bromine (179 mg 1.12 10⁻³ mol) in 1 mL CCl₄. The resulting mixture was kept at reflux temperature for 5 min. After the completion of the reaction, the solvent was removed under vacuum. The ¹H-NMR spectra were taken the crude product. According to ¹H-NMR spectra product and conversion rates were 3,6-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene (**18**) 66% (58 mg; 61% isolated yield) and 3-dibromo-1,2-bis(bromomethyl)cyclohex-1-ene (**16**) 34% (23 mg, 30% isolated yield), respectively.

4. CONCLUSIONS

The bromination reactions of 1,2-dimethylcyclohexane were examined under various reaction conditions and the effect of the reaction temperatures and the amount of the bromine on the product distributions were investigated.

Occurrence of the kinetically controlled 1,2-addition product together with 1,4-adducts at low temperatures were determined by NMR spectroscopy but the 1,2-addition product could not be isolated. It was seen that the increase in temperature caused a decrease in the amount of kinetically controlled product and an increase in the 1,4-addition products together with radicalic addition products. Increasing the amount of bromine produced an increase in the amounts of radicalic addition products and tetrabromo adduct products.

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CONFLICTS OF INTEREST

No conflict of interest was declared by the author.

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