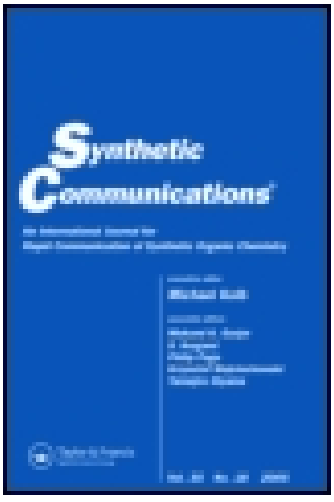

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Bromination of 4-Dichloromethyl-4-methylcyclohexa-2,5-dien-1-ones

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Abstract: Bromination of 4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-one and 4-dichloromethyl-3,4-dimethylcyclohexa-2,5-dien-1-one has been studied. The reaction conditions required for the formation of mono-, di-, and tribrominated products have been optimized.

Keywords: bromination, 4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-ones

INTRODUCTION

Geminal (di)halogenomethyl-substituted cyclohexadienones are attracting attention both as model compounds for investigation of different reactions such as the Michael addition and the Diels–Alder reaction [1]and as precursors in synthesis of drugs and pesticides.[2,3] The important examples of halogenomethyl-substituted cyclohexadienones are 9-fluoropregna-1,4-dien-3-one and its derivatives.[4–7] 9-Chloro and 9-bromo-substituted pregna-1,4-dien-3-ones are also known.[8,9] Cyclohexadienones with halogen-substituted rings are especially interesting because these compounds, on the one hand, can be used in cross-coupling reactions and, on the other hand, are attractive 1,2-dielectrophiles. Moreover, brominated cyclohexa-2,5-dienones isolated from sponges of *Latrunculia*[10–12] and *Aplisina*[13,14] families show potent

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Dedicated to the memory of Professor K. P. Butin, friend and teacher.
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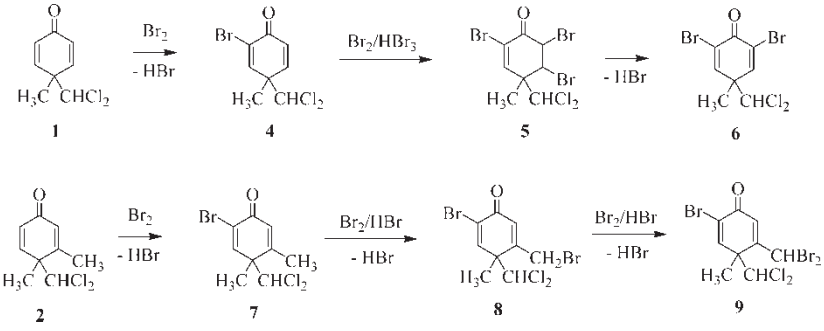
cytotoxicity and antibacterial activity. Although cyclohexa-2,5-dienones with halogens both at ring atom(s) and the one(s) attached to geminal center are attractive substrates for further modifications and can show different kinds of bioactivity, these compounds have received little attention. The main reason is the absence of good preparative approaches to these compounds because complex mixtures are usually obtained during their syntheses. Therefore, the development of simple and effective methods for the synthesis of halogenated cyclohexadienones and optimization of reaction conditions for selective preparation of the required derivatives remain important problems.

Here, we describe the optimized reaction conditions for bromination of 4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-one (**1**) and 4-dichloromethyl-3,4-dimethylcyclohexa-2,5-dien-1-one (**2**) with the goal of selective preparation of the corresponding mono-, di-, and tribrominated adducts with good to excellent yields.

RESULTS AND DISCUSSION

Scheme 1 illustrates the synthetic route to the goal compounds. Bromination of substrates **1** and **2** have been performed in CCl_4 at room temperature in the dark. Reaction products were isolated by column chromatography. Their structures have been proven by IR, UV-vis, ^{1}H NMR, and ^{13}C NMR spectroscopy data using the spectra of the corresponding 4-dibromomethyl-substituted cyclohexadienones[15] as references.

For both cyclohexadienones, the first step of bromination is substitution of the hydrogen atom in the α-position to the carbonyl group. In the case of unsymmetrical cyclohexadienone **2**, unsubstituted double bond was reacted. Cyclohexadienones **1** and **2** show the similar behavior. In contrast, the monobrominated derivatives react differently. When **1** was brominated by excess of bromine, the increase of reaction time leads to formation of tribromide



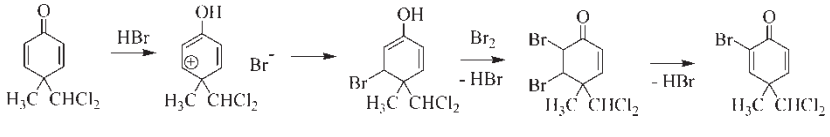
Scheme 1.

5 by addition of bromine to the unreacted double bond. The following dehydrobromination of **5** yields α,α'-dibromocyclohexadienone **6**. In the case of the methyl-substituted analogue **2**, methyl group at C(3) atom was brominated by excess of bromine with formation of 3-bromomethyl- and 3-dibromomethyl-substituted products **8** and **9**. This route of bromination is a result of acid-catalyzed enolization of **7**.

For the development of optimal procedures for preparation of mono-, di-, and tribrominated products, we have studied the effects of bromine/substrate ratio, reaction time, temperature, different additives, and other factors on the composition of the reaction mixture. It was found that bromination of cyclohexadienones **1** and **2** is accelerated by hydrogen bromide. Indeed, addition of potassium carbonate inhibited the bromination of **1** and **2**: only traces of brominated products have been found in reaction mixture after treatment for 1 week. Hydrogen bromide is evolved during the first step of bromination; that is, this reaction is autocatalytic. These data as well as the order of reactivity of two C═C double bonds in **2** support our previous assumption that the reaction mechanism can be described as nucleophilic attack by bromide anion on protonated cyclohexadienone followed by electrophilic bromination of the formed dienol (Scheme 2).

Thus, the formation of polybrominated compounds is stimulated by 1) use of bromine excess, 2) increase of reaction time, and 3) presence of acids. Oppositely, synthesis of monobrominated adducts is possible if the reaction is performed with an equimolar ratio of reagents at autocatalytic conditions. At these conditions, the formed acid concentration is not enough for effective acceleration of polybromination. With these conclusions in mind, we have found that the yield of **4** has maximum value when ratio of substrate to bromine is 1:1.25 and reaction is quenched immediately after reaction mixture decoloration. At these conditions, yield of 2-bromo-4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-one (**4**) was 82%. The corresponding dibromination product **6** has been formed with 91% yield at the substrate-to-bromine ratio of 1:2.5 and reaction mixture stirring for 1 day. According to ^{1}H and ^{13}C NMR data, **6** was contaminated by its unstable precursor **5** (product ratio was estimated to be ca. 14:1). Treatment of reaction mixture with alkaline alumina quantitatively converted enone **5** to the final product **6**.

Bromination of cyclohexadienone **2** is a more complex process. After some attempts, we have optimized the reaction conditions for the preparation of monobromide **7**, dibromide **8**, and tribromide **9** with good to excellent



Scheme 2.

yields. The synthesis of tribromide **9** has the simplest procedure: dienone **2** was treated with large excess of bromine for 1 day; yield of **9** was 92% when 25 equiv of Br_2 has been applied. Use of 1 equiv of bromine renders preparation of monobrominated cyclohexadienone **7** in 74% yield if the reaction mixture was quenched immediately after color disappearance. The most complex problem in this case is the effective synthesis of dibrominated compound **8**. The procedure applied for introduction of two bromine atoms into cyclohexadienone **1** is not effective for this case: treatment of **2** with 2.5 equiv of Br_2 leads to the mixture of **8** and **9**. Isolated yields of di- and tribrominated adducts were 32% and 43%, respectively. However, product **8** can be obtained in good yields by the fractional addition of 2 equiv of bromine. In this method, substrate **2** and bromine were stirred in the ratio of 1:1 until decoloration of reaction mixture (the reaction progress was also monitored by thin-layer chromatography TLC). When **2** was totally consumed, the reaction mixture was diluted by the addition of the same volume of solvent and 1 more equiv of bromine was added. Quenching reaction mixture immediately after the color disappeared and usual treatment allows isolation of product **8**, with yields from 60 to 80%.

CONCLUSION

In this investigation, we have optimized reaction conditions for selective bromination of 4-dichloromethyl-4-methylcyclohexa-2,5-dien-1-one (**1**) and 4-dichloromethyl-3,4-dimethylcyclohexa-2,5-dien-1-one (**2**) into their monobromides (**4**, **7**), dibromides (**6**, **8**), or tribromide **9**.

EXPERIMENTAL

^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer. All spectra were taken at 24°C in $CDCl_3$ solution using tetramethylsilane as an internal standard. IR spectra were run on an UR-20 spectrometer in Nujol. UV spectra were obtained on a Specord M-40 in ethanol solution. Alkaline Al_2O_3 (LSL 5/40) was used as a dehydrobrominating agent. The preparative column chromatography was performed on silica gel L 40/100.

4-Dichloromethyl-4-methylcyclohexa-2,5-dien-1-one (**1**) and 4-dichloromethyl-3,4-dimethylcyclohexa-2,5-dien-1-one (**8**) were prepared according to the published method.[15–17]

2-Bromo-4-(dichloromethyl)-4-methylcyclohexa-2,5-dien-1-one (4)

Bromine (0.251 g, 1.57 mmol) was added to the solution of dienone **1** (0.300 g, 1.57 mmol) in 10 ml of CCl_4. The resulting mixture was kept in

the dark at room temperature until disappearing of color (ca. 20 min). Solvent and gaseous by-products were distilled off under reduced pressure. The yellow residue was dissolved in diethyl ether, concentrated in vacuo, and redissolved in ether. The solution was shaken with alkaline Al_2O_3. Then ether was evaporated. The resulting residue was placed on the top of the silica-gel column and eluted with a benzene/diethyl ether mixture (5:0.3; R_f 0.66) to give 0.35 g (82%) of compound **4** as a clean colorless oil. After keeping for 2 days, the oil crystallized to give a white solid. It was recrystallized from chloroform/hexane mixture and then from hexane; mp 59–60°C (lit. 90–91°C);[18] UV, λ_{max}, nm (lg ε): 240 (4.30), 268 (3.67); IR: 1660, 1640, 1600 cm^{-1}; ^1H NMR: 7.41 (d, 1H, $J = 2.9$ Hz, H3), 6.99 (dd, 1H, $J = 10.1$, $J = 2.9$, H5), 6.51 (d, 1H, $J = 10.1$, H6), 5.76 (s, 1H, C*H*Cl_2), 1.54 (s, 3H, CH_3); ^{13}C NMR: 177.8 (CO), 148.8, 148.7 (C3, C5), 129.1 (C6), 126.7 (C2), 75.8 (*C*HCl_2), 51.6 (C4), 22.5 (CH_3). Anal. calcd. for $C_8H_7BrCl_2O$: C, 35.55; H, 2.59. Found: C, 35.48; H, 2.57.

2,6-Dibromo-4-(dichloromethyl)-4-methylcyclohexa-2,5-dien-1-one (6)

Bromine (0.627 g, 3.93 mmol) was added to the solution of dienone **1** (0.300 g, 1.57 mmol) in 10 ml of CCl_4. The resulting mixture was stirred for 1 day. NMR analysis of mixture showed the presence of two ketones **5** and **6** in a ratio of 1:14. Solvent and gaseous by-products were distilled off in vacuo. The yellow residue was dissolved in diethyl ether, concentrated in vacuo, and redissolved in ether. After treatment with alkaline Al_2O_3, ether was evaporated. The residue was purified by silica-gel chromatography with benzene/diethyl ether mixture (5:0.3) as eluent, R_f 0.84. The yield of dibromoketone **6** was 0.490 g (91%). The solid was dissolved in chloroform and precipitated by hexane. Mp 109–112°C (lit. 120–121°C[18], 172-174°C[19]). UV, λ_{max}, nm (lg ε): 259 (4.30); IR: 1670 cm^{-1}; ^1H NMR: 7.43 (s, 2H, H3, H5), 5.77 (s, 1H, C*H*Cl_2), 1.58 (s, 3H, CH_3); ^{13}C NMR: 171.9 (CO), 148.9 (C3, C5), 124.2 (C2, C6), 75.1 (*C*HCl_2), 53.8 (C4), 22.3 (CH_3). Anal. calcd. for $C_8H_6Br_2Cl_2O$: C, 27.50; H, 1.71. Found: C, 27.50; H, 1.65.

2,5,6-Tribromo-4-(dichloromethyl)-4-methylcyclohex-2-en-1-one (5)

^1H NMR: 7.79 (s, 1H, H3), 6.11 (s, 1H, C*H*Cl_2), 4.94 (AB system, 2H, $J = 11.7$ Hz, H5, H6), 1.56 (s, 3H, CH_3); ^{13}C NMR: 181.0 (CO), 149.4 (C3), 122.9 (C2), 77.6 (*C*HCl_2), 57.4, 54.0 (C5, C6), 53.7 (C4), 20.5 (CH_3).

2-Bromo-4-(dichloromethyl)-4,5-dimethylcyclohexa-2,5-dien-1-one (7)

Bromine (0.080 g, 0.50 mmol) was added to the solution of dienone **2** (0.1025 g, 0.50 mmol) in 5 ml of CCl_4. The resulting mixture was kept at room temperature until disappearance of color. The solvent and gaseous by-products were distilled off under reduced pressure. The yellow residue was dissolved in diethyl ether, concentrated in vacuo, and redissolved in ether. The mixture was treated with alkaline Al_2O_3. Ether was evaporated. The resulting residue was placed on the top of the silica-gel column and eluted with benzene/diethyl ether mixture (5:0.3; R_f 0.44). Product was crystallized from $CHCl_3$–hexane to afford 0.098 g (69%) of compound **7**. Mp 99–100°C; UV, λ_{max}, nm (lg ε): 248 (4.158); IR: 1660, 1640 (sh), 1610 cm^{-1}; ^1H NMR: 7.53 (s, 1H, H3), 6.23 (q, 1H, $J = 1.3$, H6), 5.87 (s, 1H, C*H*Cl_2), 2.00 (d, 3H, $J = 1.3$, C5-CH_3), 1.45 (s, 3H, C4-CH_3); ^{13}C NMR: 178.0 (CO), 158.2 (C5), 148.0 (C3), 128.1 (C6), 126.8 (C2), 75.4 (*C*HCl_2), 53.9 (C4), 23.5 (C4-*C*H_3), 18.6 (C5-*C*H_3). Anal. calcd. for $C_9H_9BrCl_2O$: C, 38.02; H, 3.16. Found: C, 37.94; H, 3.12.

2-Bromo-5-(bromomethyl)-4-(dichloromethyl)-4-methylcyclohexa-2,5-dien-1-one (8)

Bromine (40 mg, 0.25 mmol) was added to the solution of dienone **2** (54 mg, 0.25 mmol) in 0.25 ml of CCl_4 and stirred until the color disappeared (ca. 25 min). The solution of 42 mg (0.26 mmol) of bromine in 2 ml of CCl_4 was added to the resulting mixture. After 4 h, the reaction mixture was poured into diethyl ether (10 ml), alkaline Al_2O_3 was added, and it was kept, overnight. Solvent was evaporated. Residue was purified by silica-gel chromatography with benzene/diethyl ether mixture (5:0.3) as eluent, R_f 0.61. The yield of dibromoketone **8** was 57 mg (63%). Mp 79–80°C; UV, λ_{max}, nm (lg ε): 251 (3.74); IR: 1665, 1610 cm^{-1}; ^1H NMR: 7.48 (s, 1H, H3), 6.70 (s, 1H, H6), 5.99 (s, 1H, C*H*Cl_2), 4.12 (AB system, 2H, $J = 12.4$, CH_2Br), 1.62 (s, 3H, CH_3); ^{13}C NMR: 178.0 (CO), 154.8 (C5), 148.1 (C3), 132.2 (C6), 126.7 (C2), 75.3 (*C*HCl_2), 54.1 (C4), 26.8 (CH_2Br), 23.7 (CH_3). Anal. calcd. for $C_9H_8Br_2Cl_2O$: C, 29.75; H, 2.20. Found: C, 29.85; H, 2.12.

2-Bromo-5-(dibromomethyl)-4-(dichloromethyl)-4-methylcyclohexa-2,5-dien-1-one (9)

Bromine (4.0 g, 25 mmol) was added to the solution of dienone **2** (0.205 g, 1.0 mmol) in 20 ml of CCl_4. The resulting mixture was kept at room temperature for 1 day. Solvent and gaseous by-products were distilled off in vacuo. The residue was dissolved in diethyl ether, concentrated in vacuo, and redissolved in ether. The mixture was treated with alkaline Al_2O_3. Ether was

evaporated. The product was purified by precipitation from chloroform solution with hexane. Yield was 0.406 g (92%). Mp 187–188°C; UV, λ_{max}, nm (lg ε): 257 (3.12); IR: 1650, 1630, 1605 cm^{-1}; ^1H NMR: 7.35 (s, 1H, H3), 7.25 (s, 1H, H6), 6.25 (s, 1H, CH_2Br), 5.90 (s, 1H, CHCl$_2$), 1.65 (s, 3H, CH_3); ^{13}C NMR: 178.1 (CO), 158.9 (C5), 147.1 (C3), 134.2 (C6), 126.6 (C2), 74.4 (*C*HCl$_2$), 53.7 (C4), 31.1 (CHBr$_2$), 22.6 (CH_3). Anal. calcd. for $C_9H_7Br_3Cl_2O$: C, 24.43; H, 1.58. Found: C, 24.32; H, 1.49.

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