June, 1975] BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(6), 1875—1877 (1975) 1875

The Reaction of Cycloalkanones with Copper(II) Halides. II.[1)]
The Reaction of Cyclohexanones with Copper(II) Bromide

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(Received August 9, 1974)

The reaction of cyclohexanones with copper(II) bromide gave polybrominated cyclohexanediones in all cases except for the case of 3,5-dimethylcyclohexanone. Moreover, in this reaction, a pyrocatechol and a phenol derivative were obtained from 4-methyl- and 3,5-dimethylcyclohexanone respectively. The mechanism of this reaction was discussed.

Previously, the present authors reported that cyclohexanones reacted with copper(II) chloride in 50% dioxane to give polychlorinated cyclohexanediones in fairly good yields.[1,2)] In this reaction, mono-, di-, and trichlorinated cyclohexanediones were obtained in good yields by controlling the quantity of copper(II) chloride and the reaction times. However, chlorocyclohexanone, which seems to be an intermediate from cyclohexanone to the cyclohexanediones, could not be isolated. This seems to be because α- and α,α'-chloro ketones are not as easy to crystallize as bromo ketone. Consequently, in the present work, in order to confirm the reaction mechanism by isolating bromo intermediates, the reaction of cyclohexanones with copper(II) bromide instead of copper(II) chloride was carried out.

Experimental

All the melting points are uncorrected. Thin-layer chromatography was carried out on silica gel (Wakogel B-5), and detected by means of iodine or an *o*-phenylenediamine–ethanol solution. Column chromatography was carried out on silica gel (Wakogel C-100). The IR spectra were measured with a Hitachi 215 grating infrared spectrophotometer by the KBr disk method, and the UV spectra, with a JASCO ORD/UV-5 spectrometer and a Hitachi 323 recording spectrophotometer in an EtOH solution. The NMR spectra were recorded in $CDCl_3$, unless otherwise noted, with TMS as the internal standard, with a Hitachi R-20A nuclear magnetic resonance spectrometer. The chemical shifts are presented in terms of the δ value. The mass spectra were obtained with a Hitachi RMU-7M mass spectrometer at 70 eV.

Reaction of Cyclohexanones with Copper(II) Bromide. The typical procedure was in accordance with that used in the case of copper(II) chloride described previously[1)] under reflux for 0.5—2.5 hr. The reaction mixture was extracted with ether, and the extracts, after being washed and dried over Na_2SO_4, were evaporated under reduced pressure. The residue was purified by column chromatography to give the pure product.

Results and Discussion

The results are summarized in Tables 1 and 2. The NMR and IR spectra of the product from cyclohexanone showed the absorptions due to α-hydroxy-α,β-unsaturated ketone similar to those of the reaction product from cyclohexanone with copper(II) chloride; the product was identified as 3,6,6-tribromo-2-hydroxycyclohex-2-en-1-one (**3**).

In the reaction of 2- and 3-methylcyclohexanone, a product was obtained which, from its spectroscopic data, was identified as 6,6-dibromo-2-hydroxy-3-methylcyclohex-2-en-1-one (**4**), corresponding to the chloro compound.

In the case of 4-methylcyclohexanone, two products were isolated by column chromatography. The first product was determined to be 3,6-dibromo-2-hydroxy-5-methycyclohex-2-en-1-one (6), since it showed the absorptions due to an α-hydroxy-α,β-unsaturated ketone in the NMR and IR spectra and also a peak at 4.43 ppm (doublet, $J=3$ Hz) attributable to –CH(Br)– in the NMR spectrum. The second product had a peak at 2.61 ppm (singlet) attributable to aromatic methyl protons and a peak at 5.76 ppm (broad) attributable to the phenolic hydroxyl group; the ratio of their protons was 3 : 2 in the NMR spectrum. However, no peak due to aromatic protons was observed in the NMR spectrum. Accordingly, the product was identified as a hexasubstituted benzene derivative (**10**). In order to confirm that **10** can be formed through **6**, the reaction with 4-methylcyclohexanone was carried out for a longer time (2.5 hr). As a result, **6** was not obtained, but the yield of Compound **10** doubled (18%).

In the case of 3,4-dimethylcyclohexanone, it was deduced from the spectroscopic data that the product was 6,6-dibromo-2-hydroxy-3,4-dimethylcyclohex-2-en-1-one (**18**).

From the reaction of 3,5-dimethylcyclohexanone, three products were isolated by column chromatography. In the NMR spectrum of the first product, peaks were observed at 2.60 ppm (singlet) attributable to aromatic methyl protons and at 5.82 ppm (singlet) attributable to a phenolic hydroxyl group, the ratio of their protons being 6 : 1. Just as in the case of **10**, the absorption due to aromatic protons was not observed. Thus, this product was identified as a hexasubstituted benzene derivative (**17**). This identification was further confirmed by comparing the product with the sample produced from 3,5-dimethylphenol in a previously described manner.[3)] The second product showed the absorptions due to an α,β-unsaturated ketone (1683 and 1607 cm^{-1}) in the IR spectrum. There was a peak at 1.43 ppm (doublet, $J=6$ Hz) due to methyl protons and one at 2.20 ppm (singlet) due to allylic methyl protons, but there were no peaks attributable to –CH(Br)– or hydroxyl groups in the NMR

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Table 1. Reaction of cycrohexanones with copper(II) bromide

Starting material	Mole ratio per ketone	Time (hr)	Products		Yield (%)
Cycylohexanone	30	1.5	3,6,6-tribromo-2-hydroxycyclohex-2-en-1-one	(**3**)	60
2-Methylcyclohexanone	20	1.5	6,6-dibromo-2-hydroxy-3-methylcyclohex-2-en-1-one	(**4**)	14
3-Methylcyclohexanone	20	1.5	6,6-dibromo-2-hydroxy-3-methylcyclohex-2-en-1-one	(**4**)	15
4-Methylcyclohexanone	30	0.5	3,6-dibromo-2-hydroxy-5-methylcyclohex-2-en-1-one	(**6**)	28
4-Methylcyclohexanone	30	1.5	3,6-dibromo-2-hydroxy-5-methylcyclohex-2-en-1-one	(**6**)	19
			3,4,6-tribromo-5-methylpyrocatechol	(**10**)	9
4-Methylcyclohexanone	30	2.5	3,4,6-tribromo-5-methylpyrocatechol	(**10**)	18
3,4-Dimethylcyclohexanone	20	1.5	6,6-dibromo-2-hydroxy-3,4-dimethylcyclohex-2-en-1-one	(**18**)	14
3,5-Dimethylcyclohexanone	20	1.0	2,6-dibromo-3,5-dimethylcyclohexan-1-one	(**11**)	9
3,5-Dimethylcyclohexanone	20	1.5	2,6-dibromo-3,5-dimethylcyclohexan-1-one	(**11**)	9
			2,6,6-tribromo-3,5-dimethylcyclohex-2-en-1-one	(**14**)	12
			2,4,6-tribromo-3,5-dimethylphenol	(**17**)	16

Table 2. Physical properties and elemental analyses of products

Product	Mp (°C)	IR (cm^{-1})	UV (nm)	NMR (ppm)	C (%) Found (Calcd)	H (%) Found (Calcd)	[Mol. formula]
3	120—122	3413 1674 1622	301 (ε=8600)	2.97(s, 4H) 6.26(s, 1H)	(decomp.)		
4	135—138	3401 1669 1641	296 (ε=9100)	1.95(s, 3H) 2.08—3.52(m, 4H) 6.35(s, 1H)	29.59 (29.61)	2.88 (2.84)	$[C_7H_8O_2Br_2]$
6	136—137	3400 1669 1638	295 (ε=9000)	1.15(d, *J*=6 Hz, 3H), 2.09—2.64(m, 1H) 2.71(d, *J*=4.5 Hz, 1H) 2.75(d, *J*=8.2 Hz, 1H) 4.43(d, *J*=3 Hz, 1H), 6.29(s, 1H)	Found 281.8904	Calcd[a] 281.8892	$[C_7H_8O_2Br_2]$
10	125—130 (subl.)	3528 3417 1631 1581		2.61(s, 3H) 5.76(b, 2H)	Found 357.7873	Calcd[a] 357.7841	$[C_7H_5O_2Br_3]$
18	150—151 (subl.)	3402 1670 1639	296 (ε=7100)	1.17(d, *J*=6 Hz, 3H), 1.89(s, 3H) 1.53—2.85(m, 1H), 2.69(d, *J*=8.4 Hz, 1H) 2.74(d, *J*=3.2 Hz, 1H), 6.32(b, 1H)	32.44 (32.25)	3.34 (3.38)	$[C_8H_{10}O_2Br_2]$
11	175—179 (subl.)	1725		1.25(d, *J*=6 Hz, 6H) 1.31—2.43(m, 4H) 4.34 (d, *J*=11.2Hz, 2H)	Found 281.9246	Calcd[a] 281.9256	$[C_8H_{12}OBr_2]$
14	117—120	1683 1607	269 (ε=9800)	1.43(d, *J*=6 Hz, 3H), 2.20(s, 3H) 2.28—2.66(m, 1H) 2.46(d, *J*=2.5 Hz, 2H)	26.85 (26.62)	2.55 (2.51)	$[C_8H_9OBr_3]$
17	160—163 (166)[3]	3420 1545		2.60(s, 6H) 5.82(s, 1H)	26.40 (26.75)	2.06 (1.97)	$[C_8H_7OBr_3]$

a) Analyzed by high resolution mass spectrometry.

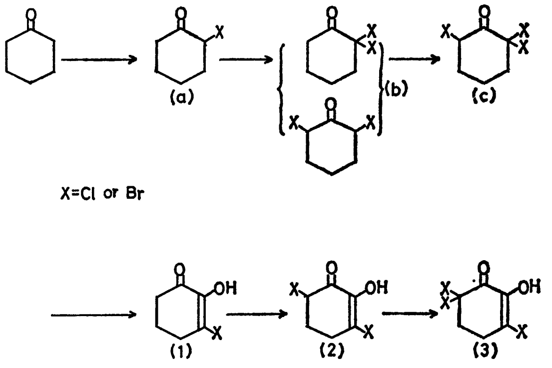
spectrum. From these data, the product was identified as 2,6,6-tribromo-3,5-dimethylcyclohex-2-en-1-one (**14**). The third product showed an absorption due to a saturated ketone (1725 cm^{-1}) in the IR spectrum, and no absorption due to unsaturated ketone in the UV spectrum. There was a peak at 1.25 ppm (doublet, *J*=6 Hz) attributable to methyl protons and one at 4.34 ppm (doublet, *J*=11.2 Hz) attributable to –CH(Br)–, the ratio of their protons being 3 : 1. Hence, the product was identified as a dibrominated cyclohexanone derivative (**11**).

In conclusion, the results of the present investigation of the reactions of cyclohexanones with copper(II) bromide can be summarized as follows: cyclohexanedione derivatives were obtained in all cases except in the case of 3,5-dimethylcyclohexanone; polysubstituted aromatic compounds were obtained in the cases of 4-methyl- and 3,5-dimethylcyclohexanone.

Now, the pathway for the formation of the polybrominated cyclohexanediones will be considered. The question of whether or not the liberated molecular bromine (Eq. 1) participates in the reaction of organic compounds with copper(II) bromide has been discussed in earlier reports:[4]

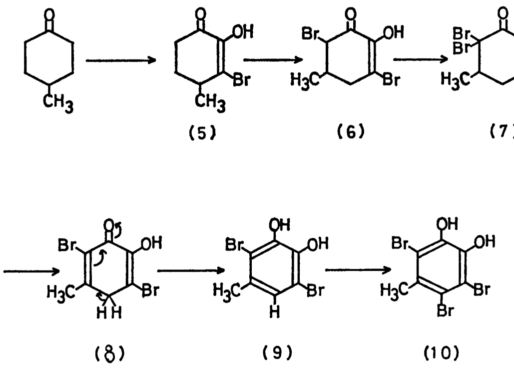
$$\mathrm{CuBr_2} \longrightarrow 1/2\mathrm{Br_2} + \mathrm{CuBr} \qquad (1)$$

Hence, the reaction of cyclohexanone with comparable amounts of bromine (15-fold molar) was carried out under the same conditions. 2,2,6,6-Tetrabromocyclohexanone [mp 118—120 °C (lit,[5]) 122—123 °C)] was obtained in a quantitative yield, but neither **1**, **2**, nor **3** was obtained. Thus, it can be concluded that the reaction leading to cyclohexanedione derivatives is a specific reaction with copper(II) bromide. Considering this finding, together with previous results in the cases of reactions with copper(II) chloride,[1] a plausible mechanism for the formation of polyhalogenated cyclohexanediones is that shown in Scheme 1. **1** may be formed by the hydrolysis and dehydration of *gem*-dihalogen of Compound (**c**), followed by enolization.



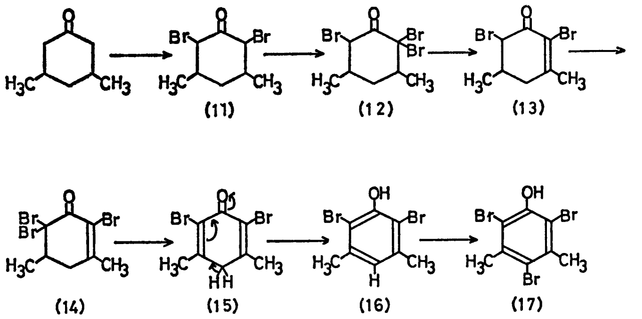
Scheme 1.

Next, the pathway to the pyrocatechol derivative will be considered. When the reaction with 4-methylcyclohexanone was stopped after only 30 min, the major product was **6**. In addition, the NMR spectrum indicated that Compound **7** [1.45 ppm (doublet, $J=6$ Hz, $-\mathrm{CH_3}$) and 2.05—2.88 ppm (multiplet, $-\mathrm{CH}-$ and $-\mathrm{CH_2}-$)] exists in the filtrate as the minor product. From all the results in the case of 4-methylcyclohexanone, the following pathway was thus demonstrated (see Scheme 2). In the first stage of the reaction, **5** was produced through the pathway shown in Scheme 1, not affected by the methyl group because the methyl group in **5** was located in the γ-position with respect to the carbonyl group. The resulting **5** was further brominated to give **6** and then **7**. **7** was then led to **8** by dehydrobromination between the *gem*-bromine and the hydrogen on the adjacent tertiary carbon because of the larger steric hindrance due to the methyl group in **7** as compared with that in Compound **3**. **8** was subjected to enolization to give a more stable aromatic compound, **9** followed by bromination to the tetrasubstituted pyrocatechol derivative (**10**).



Scheme 2.

Lastly, the pathway to the phenol derivative will be considered. When the reaction with 3,5-dimethylcyclohexanone was stopped for 1 hr and the reaction mixture then treated in the usual way, the only resulting product was **11**. Hence, we propose the following pathway for the formation of **17** (see Scheme 3). The dehydrobromination and bromination of **12**, which is derived from **11**, gives **14**. The resulting **14** was subjected to dehydrobromination, followed by enolization to give a more stable aromatic compound, **16**. **16** was then brominated to give **17**. The last step is supported by a report[6] of halogenation at the *p*-position in the reaction of a phenol derivative with copper(II) halide.



Scheme 3.

We wish to express our appreciation to Professor A. Hagitani of Rikkyo University for his kind guidance and helpful suggestions in this work. Thanks are also due to Dr. S. Hishida, Naka Works, Hitachi Ltd., for his measurement of the high-resolution mass spectra.

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