BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 48(4), 1276—1279 (1975) [Vol. 48, No. 4

The Reaction of Cycloalkanones with Copper(II) Halides. I.
The Reaction of Cyclohexanones with Copper(II) Chloride

Kyoko Nishizawa* and J. Yasuo Satoh

Department of Chemistry, St. Paul's (Rikkyo) University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171

(Received July 18, 1974)

The reaction of cyclohexanones with copper(II) chloride gave polychlorinated cyclohexanediones directly in fairly good yields. With methylcyclohexanones, in general the type of product depends on the number of methylene groups between the carbonyl group and the methyl-substituted carbon in the starting material. A possible mechanism for the reaction is discussed.

The reactions of organic compounds with copper(II) halides have been known to involve addition reactions with olefins[1] and substitution reactions with aromatic[2] or carbonyl compounds. Although substitution reactions with copper(II) chloride have also been reported for saturated or unsaturated ketones[3,4] and aldehydes,[5] monochloro-derivatives were obtained in all cases. Recently, the γ-chlorination of unsaturated ketones and aldehydes was reported by Dietl *et al.*[6] A report by Castro *et al.*[7] on both addition and substitution reactions has also appeared. In the above works, however, the reactions were carried out using only 3—5-fold molar amounts of copper(II) chloride, hence, they proceeded only to the stage of mono- or di-chlorination.

Previously, in synthesizing diosphenol from menthone with a 3-fold molar amount of iron(III) chloride according to the method of Asahina,[8] we found that a quinone derivative, which seemed to be a product of a further reaction, was obtained as a minor product, together with diosphenol.[9] It was also found that the reaction in a dioxane medium proceeded more slowly than in the case of an acetic acid medium; the reaction with copper(II) chloride also proceeded more slowly than in the case of iron(III) chloride. On the basis of these preliminary results, the reaction of cyclohexanones with excess copper(II) chloride in 50% dioxane was carried out in order to investigate the formation of the quinone derivative mentioned above. We reported[10] in a previous communication that, in this reaction, the corresponding polychlorinated cyclohexanediones were obtained in fairly good yields. In the present paper, we wish to describe the details of this reaction.

Experimental

All the melting points are uncorrected. Thin-layer chromatography was carried out on silica gel (Wakogel B-5), with detection done 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 ethanol solution. The NMR spectra were recorded in $CDCl_3$, unless otherwise noted, with TMS as the internal standard and using 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.

Materials. The 2-, 3-, and 4-methylcyclohexanone and 3,4- and 3,5-dimethylcyclohexanone were prepared from the corresponding alcohols by oxidation with sodium dichromate.[1c]

Reaction of Cyclohexanones with Copper(II) Chloride. A typical procedure was as follows: the cyclohexanone (2 g) with 20—30 times as much $CuCl_2 \cdot 2H_2O$ in 50% dioxane (v/v, 200 ml) was reacted under reflux conditions for 1—4 hr. The reaction mixture was then extracted with ether, and the extract, after being washed and dried (sodium sulfate), was evaporated under reduced pressure. The residue was purified by column chromatography.

Reaction of 2-Chlorocyclohexanone with Copper(II) Chloride. In the general manner described for the cyclohexanones, 2-chlorocyclohexanone (2 g) with $CuCl_2 \cdot 2H_2O$ (77 g) was treated under reflux for 4 hr; the usual work-up subsequently gave 1.1 g (34%) of 3,6,6-trichloro-2-hydroxycyclohex-2-en-1-one (**3**); mp 119—120 °C (lit,[12] 115—116 °C).

*Reaction of 2-Hydroxy-3-methylcyclohex-2-en-1-one (**11**) with Copper(II) Chloride.* 2-Hydroxy-3-methylcyclohex-2-en-1-one (**11**) was prepared from 2-methylcyclohexanone (10 g) according to the method of Wallach.[11a] The recrystallization of the resultant product from water containing a small amount of methanol gave needles (**11**, 2.8 g; overall yield, 22%); mp 59—60 °C (lit,[11] 62—63 °C), IR; ν_{OH} 3407 cm^{-1}, $\nu_{C=O}$ 1670 cm^{-1}, and $\nu_{C=C}$ 1640 cm^{-1}, NMR; 1.92 ppm (s, 3H), 2.03—2.85 ppm (m, 6H), and 6.22 ppm (s, 1H). By the general procedure described for the cyclohexanones, 1 g of (**11**) was refluxed with $CuCl_2 \cdot 2H_2O$ (26.8 g) for 2 hr; the reaction mixture was subsequently worked up in the usual way to give 1.1 g (70%) of 6,6-dichloro-2-hydroxy-3-methylcyclohex-2-en-1-one (**4**); mp 115—116 °C.

Reduction of 3,6,6-Trichloro-2-hydroxy-4-methylcyclohex-2-en-1-one (7) with $LiAlH_4$. The trichlorocyclohexanedione (0.5 g) in ether (15 ml) was treated with $LiAlH_4$ (0.17 g) under reflux for 1.5 hr. After the usual work-up, 0.095 g (22%) of 3,6-dichloro-2-hydroxy-4-methylcyclohex-2-en-1-one (**6**) [mp 150—153 °C (subl.)] was obtained by recrystallization from CCl_4.

Results and Discussion

The products resulting from the reaction of cyclohexanone and of its methyl derivatives with a 20-fold molar amount of copper(II) chloride are shown in Table 1, and their physical constants (Table 2). The product obtained from cyclohexanone itself showed peaks due to a diosphenolic hydroxyl group (3363 cm^{-1}) and an α,β-unsaturated ketone (1678 cm^{-1} and 1640 cm^{-1}) in the IR spectrum, and the K band (λ_{max}^{EtOH} 281 nm, $\varepsilon = 10900$) due to an α,β-unsaturated

---

* Present address: Meiji College of Pharmacy, 1-22-1 Yato-machi, Tanashi, Tokyo 188.

Table 1. Reaction of cyclohexanones with copper(II) chloride

Starting material	Mole ratio per ketone	Time (hr)	Product		Yield (%)
Cyclohexanone	20	1	3-Chloro-2-hydroxycyclohex-2-en-1-one	**(1)**	88
	20	2	3,6-Dichloro-2-hydroxycyclohex-2-en-1-one	**(2)**	72
	30	4	3,6,6-Trichloro-2-hydroxycyclohex-2-en-1-one	**(3)**	53
2-Methylcyclohexanone	20	2	6,6-Dichloro-2-hydroxy-3-methylcyclohex-2-en-1-one	**(4)**	70
3-Methylcyclohexanone	20	2	6,6-Dichloro-2-hydroxy-3-methylcyclohex-2-en-1-one	**(4)**	68
4-Methylcyclohexanone	20	2	3,6-Dichloro-2-hydroxy-5-methylcyclohex-2-en-1-one	**(5)**	23
			3,6-Dichloro-2-hydroxy-4-methylcyclohex-2-en-1-one	**(6)**	25
	30	4	3,6,6-Trichloro-2-hydroxy-4-methylcyclohex-2-en-1-one	**(7)**	65
3,4-Dimethylcyclohexanone	20	2	6,6-Dichloro-2-hydroxy-3,4-dimethylcyclohex-2-en-1-one	**(8)**	61
3,5-Dimethylcyclohexanone	20	2	6,6-Dichloro-2-hydroxy-3,5-dimethylcyclohex-2-en-1-one	**(9)**	58

Table 2. Physical properties and elemental analyses of products

Product	Mp (°C) (lit.)	IR (cm^{-1})	UV (nm)	NMR (ppm)	C (%) Found (Calcd) [Mol. formula]	H (%) Found (Calcd)
(1)	118—119 (119, 122)[12]	3290 1681 1648	271 (ε=12800)	1.94—2.28(m,2H) 2.43—2.84(m,4H) 6.34(s,1H)	48.95 (49.17) [$C_6H_7O_2Cl$]	4.88 (4.81)
(2)	98—100 (96— 98)[12]	3363 1678 1640	281 (ε=10900)	2.31—2.58(m,2H) 2.75—3.06(m,2H) 4.51(t,*J*=6Hz,1H), 6.18(s,1H)	39.71 (39.81) [$C_6H_6O_2Cl_2$]	3.37 (3.34)
(3)	119—120 (115—116)[12]	3394 1698 1638	290 (ε=10500)	2.91(bs,4H) 6.14(s,1H)	33.24 (33.44) [$C_6H_5O_2Cl_3$]	2.34 (2.34)
(4)	115—116	3402 1678 1641	286 (ε=6800)	1.77(s,3H) 2.18—2.40(m,2H) 2.64—3.45(m,2H), 6.21(s,1H)	43.12 (43.11) [$C_7H_8O_2Cl_2$]	4.32 (4.13)
(5)	78— 80	3545 1678 1634	285 (ε=7500)	1.20(d,*J*=6Hz,3H) 2.13—3.19(m,3H) 4.34(d,*J*=2.5Hz,1H), 6.17(b,1H)	43.00 (43.11) [$C_7H_8O_2Cl_2$]	4.05 (4.13)
(6)	150—153 (subl.)	3356 1688 1648	280 (ε=7500)	1.28(d,*J*=6Hz,3H), 2.20—3.25(m,3H) 4.25(dd,*J*=10.5 and 1.5Hz,1H) 6.18(s,1H)	43.08 (43.11) [$C_7H_8O_2Cl_2$]	4.16 (4.13)
(7)	119—121	3398 1696 1643	290 (ε=8300)	1.39(d,*J*=7Hz,3H) 2.74(m,3H) 6.12(s,1H)	36.88 (36.63) [$C_7H_7O_2Cl_3$]	3.22 (3.07)
(8)	142—143	3356 1690 1655	285 (ε=10900)	1.18(d,*J*=6Hz,3H), 1.71(s,3H) 1.94—2.50 (m,2H) 2.43(dd,*J*=4.5 and 18.5Hz,1H) 6.18(s,1H)	Found[a] 208.0070 [$C_8H_{10}O_2Cl_2$]	Calcd 208.0058
(9)	107—109	3399 1667 1626	289 (ε=10200)	1.30(d,*J*=7Hz,3H), 1.75(s,1H) 1.87(dd,*J*=9.7 and 14Hz,1H) 2.48(dd,*J*=4 and 14Hz,1H) 2.80—3.35(m,1H), 6.37(s,1H)	45.91 (45.96) [$C_8H_{10}O_2Cl_2$]	5.09 (4.81)

a) Analyzed by high resolution mass spectrometry.

ketone in the UV spectrum. In the NMR spectrum, the peaks appeared at 4.51 ppm (triplet, *J*=6 Hz) due to —CH(Cl)— and at 6.18 ppm (singlet) due to a phenolic hydroxyl group. From these data, the mp, and analysis, the product was identified as Compound **2**.

In the cases of 2- and 3-methylcyclohexanone, the same product was obtained. The IR and UV spectra had peaks due to an α-hydroxy-α,β-unsaturated ketone. In the NMR spectrum, a peak at 1.77 ppm (singlet) attributable to methyl protons was observed, but the peak due to —CH(Cl)— was not observed. From these data, the resulting product was identified as Compound **4**.

In the reaction of 4-methylcyclohexanone with copper(II) chloride, two products were obtained. One of these was obtained as crystals from the reaction mixture; the other was obtained from the mother liquor by column chromatography with hexane/ether (9/1). The IR and UV spectra of the former definitely indicated the presence of an α-hydroxy-α,β-unsaturated ketone, and the NMR spectrum showed a peak at 1.20 ppm (doublet, J=6 Hz) due to methyl protons and a peak at 4.34 ppm (doublet, J=2.5 Hz) due to –CH(Cl)–. This product was concluded to be Compound **5** on the basis of the above data. The other product also showed the presence of an α-hydroxy-α,β-unsaturated ketone in the IR and UV spectra. The NMR spectrum had a peak at 1.28 ppm (doublet, J=6 Hz) due to methyl protons and a peak at 4.25 ppm (double-doublet, J=10.5 and 1.5 Hz) due to –CH(Cl)–. Hence, this product must have the structure of **6**.

In the reaction with a 20-fold molar amount of the reagent, 2- and 3-methylcyclohexanone gave a *gem*-dichloro derivative, while cyclohexanone and 4-methylcyclohexanone did not give such a product with a *gem*-dichloro-function. It was considered that, in the cases of cyclohexanone and 4-methylcyclohexanone, their reactive carbon in the α-position with respect to the carbonyl group should make them capable of yielding the products mentioned above, just as in the cases of 2- and 3-methylcyclohexanone. Therefore, the reaction was attempted using a 30-fold molar amount of copper(II) chloride. The product resulting from cyclohexanone was identified as Compound **3**, with the *gem*-dichloro-function, from the facts that it did not show a peak due to –CH(Cl)– in the NMR spectrum and that the IR and UV spectra had peaks attributable to an α-hydroxy-α,β-unsaturated ketone. Furthermore, the product from 4-methylcyclohexanone was found to be Compound **7** inasmuch as its IR and UV spectra indicated an α-hydroxy-α,β-unsaturated ketone, while its NMR spectrum showed a peak at 1.39 ppm (doublet, J=7 Hz) due to methyl protons and another peak at 6.12 ppm (singlet due to a phenolic hydroxyl group.

These results indicate that, in the reaction of monomethylcyclohexanone with copper(II) chloride, in general the type of product depends on the number of methylene groups between the carbonyl group and methyl-substituted carbon in the starting material. In the case of no or only one methylene group—that is, 2- or 3-methylcyclohexanone—the product obtained in either case was a *gem*-dichloroderivative—that is, of Type B, with a vinyl methyl group. In the case of two methylene groups—that is, 4-methylcyclohexanone—the product obtained was a trichloro-derivative—that is, of Type A, with a methyl group at the 4-position.

Therefore, in order to find out whether this reaction could occur in the cases of dimethylcyclohexanones, the reactions of 3,4- and 3,5-dimethylcyclohexanone with a 20-fold molar amount of the reagent were carried out under the same conditions. Compounds **8** and **9** were thus obtained from the 3,4- and 3,5-dimethyl derivatives respectively. Consequently, it was found that a reaction like that in the case of the monomethyl derivatives also occurred in the case of such dimethylcyclohexanones. Moreover, from the fact that the product obtained was Type B in the case of 3,4-dimethylcyclohexanone, it was found that the generality that the oxygen group enters the 2-position, not the 6-position, is also applicable in this case.

Now, on the basis of these results, let us consider the pathway for the formation of Type A. It has previously been reported[3] that an α-chlorination occurs easily *via* the enol complex in the reactions of saturated ketones with copper(II) chloride. It was found that, in steroidal ketone, a *gem*-dichloro derivative was obtained together with an α-chloro derivative.** Hence, the present reaction would be initiated by an attack on the α-carbon in cyclohexanone with copper(II) chloride, followed by α,α- and/or α,α′-dichlorination.

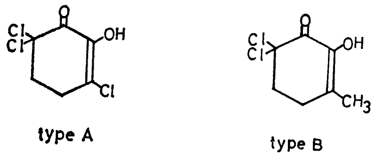

Fig. 1.

Therefore, the α-chlorination product (**a**)—namely, 2-chlorocyclohexanone—, was treated under the same conditions. It was found that oxidative chlorination occurred to give Compound **3**, just as in the case of cyclohexanone. To ascertain the intermediate product in the oxidative chlorination of cyclohexanone, the reaction with a 20-fold molar amount of the reagent was stopped after the mixture had been refluxed for only 1 hr under the same conditions. The product was isolated from the reaction mixture in the usual way and identified as Compound **1** from its spectroscopic data and from its melting point. Moreover, Compounds **2** and **3** were obtained in fairly good yields from the reaction of cyclohexanone with 20-fold molar and 30-fold molar amounts of reagents respectively, as has been mentioned before.

The foregoing results suggest that, after the α-monochlorination product (**a**) is chlorinated to give α,α,α′-trichlorinated cyclohexanone (**c**) through α,α- and/or α,α′-dichlorinated derivatives (**b**), the resulting product (**c**) is hydrolyzed to give 3-chloro-2-hydroxycyclohex-2-en-1-one (**1**). In the later stages, **1** is further chlorinated at the α-position with respect to the carbonyl group to give **3** through **2**. In the case of 4-methylcyclohexanone, the reaction proceeds according to the pathway described above, not being affected by the methyl group, for the methyl group in the methylcyclohexanone is located in a γ-position with respect to the carbonyl group. Hence, this is the pathway proposed for the formation of Type A (Fig. 2):

Next, let us consider the pathway for the formation

** Unpublished data: in the reaction of 5α-cholestan-3-one with copper(II) chloride under the same condentions, 2α-chloro- and 2,2-dichloro-5α-cholestan-3-one were obtained.

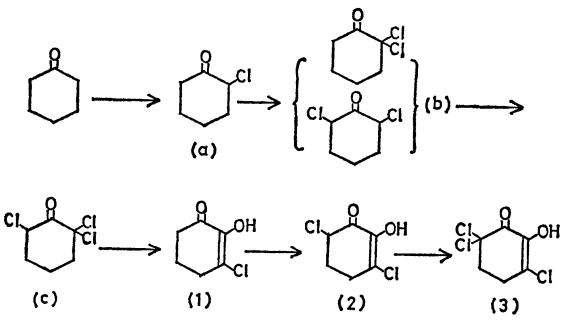

Fig. 2.

of Type B. In the cases of 2- and 3-methylcyclohexanone, the same product (**4**) was obtained. In these cases, the reaction also proceeds *via* Type (**1**), according to Fig. 2. Hence, Type (**1**) —namely, 2-hydroxy-3-methylcyclohex-2-en-1-one (**11**)—was prepared by the method of Wallach,[11a)] and the product (**11**) was reacted with copper(II) chloride under the same conditions to give Compound **4**. Also, the reaction of 2-methylcyclohexanone with a 20-fold molar amount of copper(II) chloride was stopped after 15 min under the same conditions. The NMR spectrum of the reaction mixture showed that Compounds **4** and **11** had already been produced. Consequently, 2- and 3-methylcyclohexanone were each refluxed with a 10-fold molar amount of the reagent for 7 hr under the same conditions. The NMR spectra of the reaction mixtures suggested that Compound **11** was quantitatively produced in both cases. Therefore, it was found that Compound **11** was an intermediate of the reaction for the formation of Type B.

It was considered that, in these cases, the reaction also proceeded *via* the enol complex in the earlier stage. Then, in the case of 2-methylcyclohexanone, α-chlorination occurs preferentially at C_6 in the methylcyclohexanone, in contrast with the case of halogenation with molecular halogen,[11a)] because the steric hindrance at C_6 is smaller than that at C_2 in the formation of the enol complex. This assumption is supported by the findings that Compound **4**, derived from the C_6-chlorination product, not from the C_2 product, was isolated in a 70% yield, and that no phenol derivative, such as would be derived from the C_2-chlorination product, could be isolated. The α-chlorinated product (**a′**) is dichlorinated at C_6, followed by hydrolysis to give **10**. The dione (**10**) is enolized in the direction of the methyl group to give Compound **11** because of the stabilization by hyperconjugation of the methyl group.

In the case of 3-methylcyclohexanone, the methyl group should have no influence on the earlier stage of the reaction, just as in the case of 4-methylcyclohexanone, because the methyl group was located in the β-position with respect to the carbonyl group in the starting material, in contrast with the 2-methylcyclohexanone. Therefore, it was considered that the pathway were: (**a″**)→(**b″**)→(**10**)→(**11**)→(**2″**)→(**4**) and/or (**a″**)→(**b″**)→(**c″**)→(**2″**)→(**4**). The former pathway, however, is more reasonable because Compound **11**, as an intermediate, was obtained from the reaction of 3-methylcyclohexanone with a 10-fold molar amount of copper(II) chloride, as has been mentioned above. Hence, the pathway for the formation of Type B may be described as follows:

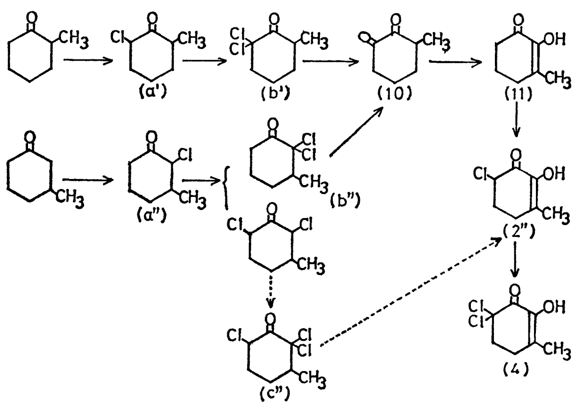

Fig. 3.

On the synthesis of the compounds obtained from the present work, there have been only a few reports. One of these is by Sucrow and Wanzlick,[12)] in which 3,6,6-trichloro-2-hydroxycyclohex-2-en-1-one (**3**) was synthesized *via* Compounds **1** and **2** from cyclohexane-1,2-dione in several steps. The present work, however, has demonstrated that Compound **3** can be synthesized in one step from readily available cyclohexanone and copper(II) chloride. Thus, it can be concluded that this reaction constitutes an improved method for the synthesis of polychlorinated cyclohexanediones.

The authors wish to thank 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.

References

1) W. C. Baird, JR., J. H. Surridge, and M. Buga, *J. Org. Chem.*, **36**, 3324 (1971).

2) H. P. Crocker and R. Walser, *J. Chem. Soc.*, **1970**, 1982.

3) J. K. Kochi, *J. Amer. Chem. Soc.*, **77**, 5274 (1955).

4) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963); E. M. Kosower and G.-S. Wu, *ibid.*, **28**, 633 (1963).

5) A. Lorenzini and C. Walling, *ibid.*, **32**, 4008 (1967).

6) H. K. Dietl, J. R. Normark, D. A. Payne, J. G. Thweat, and D. A. Young, *Tetrahedron Lett.*, **1973**, 1719.

7) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **30**, 587 (1965).

8) Y. Asahina and S. Mitsuhori, *Yakugaku Zasshi*, **482**, 255 (1922).

9) M. Hirose, K. Nishizawa, S. Yamamoto, A. Hagitani, and J. Y. Satoh, Abstract of 15th Symposium on the Chemistry of Terpens, Essential Oils and Aromatics, Osaka, Japan, November, 1971, p. 173.

10) J. Y. Satoh and K. Nishizawa, *Chem. Commun.*, **1973**, 83.

11) (a) O. Wallach, *Ann. Chem.*, **414**, 314 (1918). (b) K. Sato, S. Inoue, and M. Ōhashi, This Bulletin, **47**, 2519 (1974).

12) W. Sucrow and H.-W. Wanzlick, *Chem. Ber.*, **92**, 2516 (1959).