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THE REACTION OF ALKYLCYCLOHEXANONES WITH COPPER(II) BROMIDE AND 1,2-GLYCOLS

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Alkylcyclohexanones react with copper(II) bromide and 1,2-glycols to give alkyl-substituted 2,3-dihydro-1,4-benzodioxin and 1,4,5,8-tetraoxa[4,4,4]propellane derivatives.

Copper(II) halides have long been used as halogenating agents for organic compounds, undergoing addition reactions with olefins and substitution reaction with aromatic hydrocarbons and carbonyl compounds.[1] In a previous communication,[2] we reported that the reaction of cyclohexanones and steroidal ketones with ethylene glycol in the presence of small amounts of copper(II) halide (0.1 mol equiv.) gave the acetals smoothly in quantitative yields, and that the reaction of steroidal ketones with 5 mol equiv. of copper(II) halide in a mixed solvent consisting of the glycol and commercial dioxane (1 : 1) under refluxing conditions occurreds resulting in their acetalisation accompanied by α-halogenation. In the present work, it was found that the latter reaction for alkylcyclohexanones gave 2,3-dihydro-1,4-benzodioxin derivatives. These compounds have been synthesized from pyrocatechol,[3] but the direct synthesis of the derivative from cyclohexanones has not been reported.

The typical reaction procedure for 2-methylcyclohexanone was as follows: To a solution of 2-methylcyclohexanone (1g, 8.93 mmol) in ethylene glycol (40 ml) was added copper(II) bromide (9.95g, 44.65 mmol). After heating at 70°C for 5 h, the reaction mixture was poured into water. Ether extraction and column chromatography gave 5-methyl-2,3-dihydro-1,4-benzodioxin (1). When the temperature was raised to 110°C, the reaction completed in 10-60 min (Table 1).

As the other 1,2-glycols, cis- and trans-cyclohexane-1,2-diols, glycerol, and 3-chloro-1,2-propanediol were used. Since the cyclohexanediols are crystalline materials, the reaction was carried out in medium of diglyme. In the case of

glycerol, 1,4-benzodioxin derivatives having a hydroxymethyl group in the 2- and 3-position (1 : 1) were formed, but the reaction at C_1-OH and C_3-OH of glycerol did not occur (Table 2).

Table 1. Reaction of alkylcyclohexanones at 70°C

Starting materials	Time (h)	Products		Isolated yields (%)
2-Methylcyclohexanone	8	5-Methyl-2,3-dihydro-1,4-benzodioxin	(1)	41
2-Isopropyl- "	8	5-Isopropyl- "	(2)	40
2-Cyclohexyl- "	18	5-Cyclohexyl- "	(3)	70
3,5-Dimethyl- "	9	5,7-Dimethyl- "	(4)	40
Menthon	7	5-Isopropyl-8-methyl- "	(5)	64

Table 2. Reaction of 2-methylcyclohexanone at 120°C for 1h

1,2-Diols	Products		Isolated yields (%)
trans-Cyclohexane-1,2-diol	trans-6-Methyl-1,2,3,4,4a,10a-hexahydrodibenzodioxin	(6)	55
cis-Cyclohexane-1,2-diol	cis-6-Methyl-1,2,3,4,4a,10a-hexahydrodibenzodioxin	(7)	45
Glycerol	2- and 3-Hydroxymethyl-5-methyl-2,3-dihydro-1,4-benzodioxin (1:1-mixture)	(8)	40
3-Chloro-1,2-propanediol	2- and 3-Chloromethyl-5-methyl-2,3-dihydro-1,4-benzodioxin (1:1-mixture)	(9)	26

Moreover, it was found that, even in a short time, appreciable amounts of 5-methyl-2,3-dihydro-1,4-benzodioxin together with 9-methyl-1,4,5,8-tetraoxa[4,4,4]-propellane and bromoacetal of 2-methylcyclohexanone could be obtained (Table 3).

Table 3. Reaction of 2-methylcyclohexanone at 70°C

Time (h)	Products		Isolated yields (%)
0.5	2-Bromo-2-methylcyclohexanone ethylene acetal (containing a slight amount of 6-bromo-deriv.)	(10)	60
	9-Methyl-1,4,5,8-tetraoxa[4,4,4]propellane	(11)	2
2	10		16
	11		19
	1		16
8	10		8
	1		41

On the synthesis of the tetraoxapropellane derivative, there has only one report, that by Jaeger and Smith,[4] in which 1,4,5,8-tetraoxa[4,4,4]propellane was synthesized only in 0.5-2% yield from cyclohexane-1,2-dione with ethylene glycol under acidic conditions. Hence, the synthesis of the propellane derivative according to the present method at 55-60°C for 2-2.5 h was attempted with 2-isopropyl- and 2-cyclohexylcyclohexanones, and menthon. These results are shown in

Table 4.

Table 4

Starting materials	Products		Isolated yields (%)
2-Isopropyl-cyclohexanone	2-Bromo-2-isopropylcyclohexanone ethylene acetal (containing a slight amount of 6-bromo-deriv.)	(12)	8
	9-Isopropyl-1,4,5,8-tetraoxa[4,4,4]propellane	(13)	20
	2		21
2-Cyclohexyl-cyclohexanone	2-Bromo-2-cyclohexylcyclohexanone ethylene acetal (containing a slight amount of 6-bromo-deriv.)	(14)	12
	9-Cyclohexyl-1,4,5,8-tetraoxa[4,4,4]propellane	(15)	34
	3		17
Menthon	2-Bromo-2-isopropyl-5-methylcyclohexanone ethylene acetal (containing a slight amount of 6-bromo-deriv.)	(16)	6
	12-Isopropyl-9-methyl-1,4,5,8-tetraoxa[4,4,4]-propellane	(17)	8
	5		51

In the case of 3-oxo steroid, while this reaction proceeds quantitatively to its α-bromoacetalization as mentioned in a previous paper, further reaction did not occur even on raising the temperature to 120°C. This seems to be due to a large steric hindrance which arises between the propellane ring about to be formed and the C_{10}-methyl group or ring B in the steroid.

Compared with the usual procedure for the synthesis of the 1,4-benzodioxin and 1,4,5,8-tetraoxa[4,4,4]propellane derivatives, we believe that the present reaction is an improved one-step method for forming these two derivatives, having alkyl groups in the desired positions. Moreover, the reaction may be applicable to the synthesis of heterocyclic compounds such as piperoxane derivatives, which are diagnostic agents for detection of epinephrine-producing tumors, and also to the synthesis of alkyl-substituted pyrocatechol derivatives by cleavage of the C-O bond in the dioxin derivative with boron tribromide.

References and Notes

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5) All of these reactions were monitored by TLC and NMR measurements. The products (1∿9, 11, 13, 15, and 17) were adequately characterized by elemental analysis (liquid dioxin derivatives were determined as their bromo-derivatives) and spectroscopies. The structure of the propellane derivatives was determined by the half-height-width (≃50Hz) of AA'BB' signal due to -O-CH_2-CH_2-O- protons (B. Fuchs, Tetrahedron Lett., 1970, 1747). Bp (or mp) and NMR data of the products are give below. (1); bp 68-69°C/1.2 mm [lit. 74°C/1.4 mm: A. W. Archer, et al., J. Chem. Soc. (B), 1971, 1231]; 6,7,8-tribromo-derivative, mp 139.5-140°C. (2); 1.16(d,6H,J=7Hz,2Me), 3.17(sep,1H,J=7Hz,CH), 4.14(s,4H,CH_2-CH_2), 6.58(s,3H,Ar-H); the sample quantity was so small, that the bp could not be determined; 6,7,8-tribromo-derivative, mp 110-112°C; Anal. for $C_{11}H_{11}O_2Br_3$: C, 31.84, H, 2.67%. Found: C,31.79, H, 2.62%. (3); 1.19-2.25(m,10H,cyclohexyl-H), 2.85(m,1H,Benzal-H), 4.07(s,4H,CH_2-CH_2), 6.62(s,3H,Ar-H); mp 63.5-64.5°C; Anal. for $C_{14}H_{18}O_2$:C, 77.03, H, 8.31%. Found: C, 76.99, H, 8.34%. (4); 2.10 (s,3H,Me), 2.17(s,3H,Me), 4.13(s,4H,CH_2-CH_2), 6.39(s,2H,Ar-H); bp 68.5°C/2 mm; 6.8-dibromo-derivative, mp 118-119.5°C; Anal. for $C_{10}H_{10}O_2Br_2$: C, 37.29, H, 3.13 %. Found: C, 37.34, H, 3.16%. (5); 1.16(d,6H,J=7Hz,2Me), 2.10(s,3H,Me), 3.17 (sep.1H,J=7Hz,CH), 4.15(s,4H,CH_2-CH_2), 6.61(s,2H,Ar-H), bp 107°C/7 mm; 6.7-dibromo-derivative, mp 90-92°C; Anal. for $C_{12}H_{14}O_2Br_2$: C, 41.18, H, 4.03%. Found: C, 41.10, H, 3.98%. (6); 0.75-2.27(m,8H,cyclohexyl-H), 2.16(s,3H,Me), 3.26(m,2H, 2CH), 6.56(s,3H,Ar-H); mp 96-98°C; Anal. for $C_{13}H_{16}O_2$: C, 76.44, H, 7.90%. Found : C, 76.37, H, 7.91%. (7); 0.80-2.30(m,8H,cyclohexyl-H), 2,18(s,3H,Me), 4.07(m, 2H,2CH), 6.58(s,3H,Ar-H); bp 112°C/3 mm; Anal. for $C_{13}H_{16}O_2$: C, 76.44, H, 7.90%. Found: C, 76.34, H,7.96%. (8); bp 127°C/2 mm(lit. 129-130°C/1 mm: J. R. Geigy, Brit. 565,573; C. A., 40, 5073[1]). (9); 112°C/2 mm (lit. 137°C/13 mm: J. R. Geigy, Swiss, 233,683, C. A., 43, 4304c). (11); 0.90(d,3H,J=6.5Hz,Me), 1.30-2.60 (m,7H,cyclohexyl-H), 3.35-4.67(m,8H,2CH_2-CH_2); mp 101-102.5°C; Anal. for $C_{11}H_{18}O_4$: C, 61.66, H, 8,47%. Found: C, 61.65, H, 8.42%. (13); 0.88(d,3H,J=7Hz,Me), 0.95(d,3H,J=7Hz,Me), 1.14-2.70(m,8H,cyclohexyl-H and CH), 3.30-4.71(m,8H,2CH_2-CH_2); mpl43.5-145°C; Anal. for $C_{13}H_{22}O_4$: C, 64.44, H, 9.15%. Found: C, 64.39, H, 9.10%. (15); 0.75-2.57(m,18H,2cyclohexyl-H), 3.29-4.56(m,8H,2CH_2-CH_2); mp 103-105°C; Anal. for $C_{16}H_{26}O_4$: C, 68.06, H, 9.28%. Found: C, 68.10, H, 9.22%. (17); 0.88(d,6H,J=7Hz,Me), 0.95(d,3H,J=6.5Hz,Me), 1.35-2.60(m,7H,cyclohexy-H and CH), 3.23-4.56(m,8H,2CH_2-CH_2); mp 88-90°C; Anal. for $C_{14}H_{24}O_4$: C, 65.60, H, 9.44%. Found: C, 65.57, H. 9.40%.

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