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Effect of Crown Ether in the Reduction of Ketones with Sodium Borohydride in Aromatic Solvent

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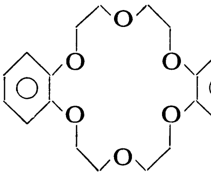
Cyclic polyethers, firstly synthesized by Pedersen[1a] and known as crown ethers, have been attracted much attention because of their unusual capability to form stable complexes with a variety of metallic or non-metallic cations.[1] Asides of their utility in physico-chemical phenomena[1b] they are also interesting in the application of the function to organic synthesis. Pedersen[1a] reported a successful saponification of the sterically hindered esters of 2,4,6-trimethylbenzoic acid with potassium hydroxide in aromatic hydrocarbon in the presence of dicyclohexyl-18-crown-6. Subsequent papers[2] have revealed dominating feature of the cyclic polyethers in enhancement of anion reactivity by complex formation with a counter cation in low dielectric solvents. In this paper, we report an effectiveness of dibenzo-18-crown-6 (I) in sodium borohydride reduction of some ketones in aromatic hydrocarbon.



I

Results and Discussion

Effect of the Addition of Various Ethers. A ketone (0.12 mol) was allowed to react with sodium borohydride (0.03 mol) in 100 ml toluene for 5 hr under reflux in the presence of three ethereal additives (0.03 mol). The results for four ketones were illustrated in Table 1. Table 2 shows the influence of relative amount of I to sodium borohydride in the reduction of cyclohexanone. The presence of 5 mol% of I to the reducing agent was found to be almost as effective as equimolar combination of I. Because of the low solubility of sodium borohydride under the conditions, the ratio of I to sodium borohydride above 5 mol% does not have a practical importance. Use of potassium borohydride required a prolonged reaction period. Sullivan and Hinckley[3] reported that in the reduction of acetophenone tricaprylmethylammonium borohydride afforded a 20% yield of the corresponding alcohol at 25 °C (4 hr) and a 8% at 65 °C (2 hr) in benzene solvent.

Present reduction which was carried out at higher temperature and with longer reaction time gave much improved yields, but was inevitably accompanied by the formation of by-product. The by-product in the reduction of cyclohexanone was found to be mostly consisted of 2-(cyclohexen-1-yl)-cyclohexanol (III, a mixture of *cis* and *trans* isomers) and the corresponding ketone(II). Table 3 suggests the occurrence of base-catalyzed condensation of the ketone. 3,3,5-Trimethyl-

TABLE 1. EFFECT OF ETHEREAL ADDITIVES ON THE REDUCTION OF KETONES[a]

Ketone		Product,[b] %		
		I	Diglyme	Dimethoxy-ethane
Acetophenone	Alcohol	49	42	23
	Ketone	0	38	40
	Residue	28	12	13
Cyclohexanone	Alcohol	50	28	19
	Ketone	0	32	56
	Residue	37	17	8
Methyl *n*-amyl ketone	Alcohol	41	27	14
	Ketone	3	9	34
	Residue	29	22	18
Methyl *iso*-propyl ketone	Alcohol	23	11	0
	Ketone	63	74	78
	Residue	10	6	5

a) Solvent; toluene, reflux for 5 hr.
b) The values show weight percent to the amount of ketone utilized.

TABLE 2. INFLUENCE OF RELATIVE AMOUNT OF I TO $NaBH_4$ IN THE REDUCTION OF CYCLOHEXANONE

Product[a] %	Ratio of I to $NaBH_4$							
	1	0.5	0.25	0.125	0.05	0.02	0.01	0
Alcohol	50	43	40	47	42	13	0	0
Ketone	0	0	0	1	2	45	84	85
Residue	37	48	42	48	43	25	3	trace

a) See footnote in Table 1.

TABLE 3. TIME DEPENDENCE IN THE REDUCTION OF CYCLOHEXANONE[a]

Time, min	Product,[b] %			
	Ketone	Alcohol	III	II
10	97	3	0	0
20	47	33	30	0
40	7	58	27	8
60	0	56	16	28
90	0	57	6	37

a) Equimolar amount of $NaBH_4$ was used.
b) The values show relative peak areas of gas chromatogram for undistilled raw products.

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[3] E. A. Sullivan and A. A. Hinckley, *J. Org. Chem.*, **27**, 3731 (1962).

TABLE 4. STEREOCHEMICAL OUTCOME IN THE REDUCTION OF CYCLIC KETONES

Ketone	Conditions			Products,[a] %			
				Ketone	Alcohol		
	I/$NaBH_4$	Time, hr	Solvent[b]		*cis*(*exo*)[c]	*trans*(*endo*)[c]	*cis*/*trans* (*exo*/*endo*)[c]
4-Methylcyclohexanone	1	5	T	0	26	74	26
4-*t*-Butylcyclohexanone	1	5	T	3	22	75	23
	0.5			0	21	79	21
3,3,5-Trimethylcyclohexanone	1[d]	5	T	77	10	13	44
	1			31	52	17	75
	1			15	68	17	80
	0.1			25	62	13	83
	0.05			27	56	16	78
2-Norbornanone	1	5	T	84	5	11	31
	1	9	T	78	6	16	29
	1	3.5	X	41	20	39	34
	1	5	X	4	31	65	32

a) Weight percent for distillate. b) T=toluene, X=*o*-xylene. c) For 2-norbornanone.
d) The reaction was carried out at 100 °C, and the others were under reflux.

cyclohexanone was more resistant to the reduction than less hindered substituted cyclohexanones; 4-methyl- and 4-*t*-butylcyclohexanone (Table 4). The reduction of 2-norbornanone required a higher reaction temperature to achieve a good conversion and camphor did not react to a measureable extent.

Effect of I on the Stereochemical Course. It is known that the stereochemical course of sodium borohydride reduction is subjected to various factors, such as steric[4] or polar effect[5] in substituted ketones, as well as the nature of solvent.[6] The isomer distributions of the product alcohols obtained in the reduction of substituted cyclohexanones and 2-norbornanone were tabulated in Table 4. Reduction of 4-methyl- and 4-*t*-butylcyclohexanone yielded alcohols in 74 and 77% abundance of *trans* isomer, respectively, which are in good accordance with the reported *trans* contents of 76 and 78% for the reductions in 2-propanol.[5]

In the borohydride reduction of 3,3,5-trimethylcyclohexanone the *cis* alcohol was always an unfavorable isomer in the product and its abundance varies from 27 to 45% depending on the solvent utilized.[6] On the other hand, the *cis* isomer was found to become the predominant product in the present reduction. The present results can be explained in terms of a smaller effective size of reducing agent in nonpolar solvent; toluene. The increased yield (29—34%) of *exo* alcohol from 2-norbornanone as compared to the result in 2-propanol (14%)[4b] can again be accommodated with the idea.

The observed order of facility of reduction in toluene, cyclohexanone$\approx$4-substituted cyclohexanones$>$3,3,5-trimethylcyclohexanone ($\approx$methyl isopropyl ketone)$>$ 2-norbornanone$\gg$ camphor, also suggests that an unsolvated borohydride anion in toluene still suffers the similar kind of steric hindrance as observed in conventional solvent,[4b] possibly because of close proximity of sodium ion complexed with the cyclic polyether to borohydride anion.

Experimental

Materials. Dibenzo-18-crown-6-(2,3,11,12-dibenzo-1, 4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene) was prepared by the procedure described by Pedersen,[1a] mp 163.2—164.5 °C (lit,[1a] 164 °C). 2-Norbornanone[7] and methylisopropyl ketone[8] were obtained by the standard methods. Other liquid ketones used were commercial products and distilled prior to use. Sodium borohydride and camphor were used without purification.

Procedures. A typical procedure is as follows. A mixture of I (10.8 g, 0.03 mol), finely pulverized sodium borohydride (1.13 g, 0.03 mol) and dry toluene (100 ml) was refluxed for 0.5 hr under stirring. Cyclohexanone (11.8 g, 0.12 mol) in toluene (20 ml) was added in a period of 10 min and the mixture was refluxed for 5 hr under stirring. The reaction mixture was cooled and hydrolyzed by addition of dil. hydrochloric acid and let stand at 0 °C. Crystalline I precipitated was removed by filtration and the water layer was extracted three times with ether. The combined organic layer was neutralized, dried and concentrated. Distillation of the concentrate yielded cyclohexanol (6.7 g, 50% bp 89—92 °C/80 mmHg) and a residue (4.4 g). A distillate from the residue (3.9 g, bp 80—100 °C/2 mmHg) was found to be composed mainly of *cis*- and *trans*-2-(cyclohexen-1-yl)-cyclohexanol and small amounts of the corresponding ketone and an unidentified compound by gas chromatography (compared with authentic specimen[9]). Extent of the reduction and isomer ratios of the products were determined by gas chromatography on Ucon Oil HB5100 10%-Celite column or 1,2,3-tris(2-cyanoethoxy)propane 10%-Shimalite column (for isomers of 4-methyl- and 4-*t*-butylcyclohexanol).

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