Reduction of α,α-Dihaloketones with Electrophilic and Nucleophilic Reducing Agents

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The reduction of α-halocarbonyl compounds has often been used as a simple high-yielding method for the preparation of halohydrins. However, one complication that can severly limit this method comes from concomitant hydrogenolysis of the carbon-halogen bond. For example, catalytic reduction of these systems leads to a preponderance of hydrogenolysis products[2]. Likewise, nucleophilic reducing agents are known to cleave carbon-halogen bonds while reducing the adjacent carbonyl group[3-8]. On the other hand, electrophilic reducing agents, e.g. diborane, have been reported to react so slowly with α-haloaldehydes so as to render this method synthetically useless for the preparation of halohydrins[9].

In connection with our ongoing investigations into the acid-catalyzed rearrangement of aryldihalopropanols[10-15], need for these compounds arose. Surprisingly, the literature provides few examples of reductions of α,α-dichloroketones and only a single, unsatisfactory, case where an α,α-dibromoketone had been reduced without causing hydrogenolysis. We report, herein, the results of an investigation into the reduction of α,α-dihaloketones using a variety of reducing agents.

Since sodium borohydride had proven to be highly satisfactory in our reduction of 1-(*o*-chlorophenyl)-2,2-dichloro-1-propanone[14], initial efforts to reduce the analogous dibromoketone **1c** focused on mild nucleophilic reducing agents. Unfortunately, sodium borohydride reduction of **1c** led to an equimolar mixture of the monobromoalcohol **3c** and the dibromoalcohol **2c**. Efforts to separate this mixture were only moderately successful, however, and only a 10% yield of **2c** was realized. Consequently, lithium tris[*t*-butoxy]aluminum hydride was used in an attempt to prevent hydrogenolysis through steric effects. However, even at −20 °C in *i*-propyl alcohol and with equimolar concentrations, these modifications resulted in no substantial improvement in preventing formation of the hydrogenolysis product: **3c** was found in 40-50%

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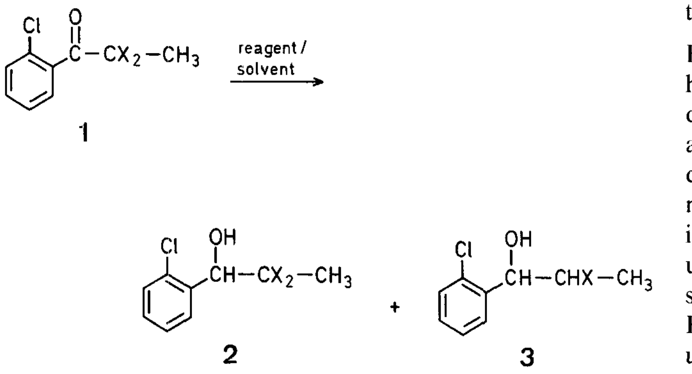
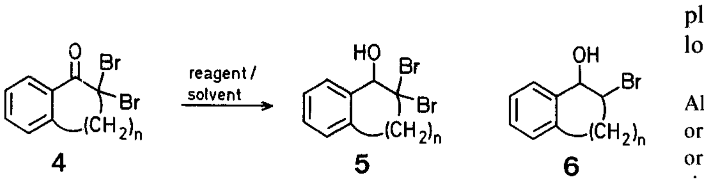
yield. K-Selectride reduction of **1c** also led to **3c** in a very high yield. With these results, our attention was directed toward electrophilic reducing agents.

Diisobutylaluminum hydride (DIBAH) has displayed many desirable characteristics as a metal hydride reducing agent, most important of which is its selectivity at reduced temperature[15,16]. When DIBAH was caused to react with **1c** in hexane at room temperature a 90% yield of **2c** resulted and, most importantly, no hydrogenolysis product could be detected. Examination of a variety of additional halogenated ketones **1** and **4**, Tables 1 and 2, revealed that DIBAH reductions took place rapidly, conveniently and in high yield.



Scheme A



Scheme **B**

The rather facile nature of this reduction was somewhat unexpected in view of the previously reported failures involving the electrophilic reduction of the alpha-trihalogenated aldehyde, chloral, with diborane[17,18]. Therefore, we initiated a study of the reduction of **1c** with diborane (B_2H_6) in tetrahydrofuran and borane:dimethyl sulfide [BMS; $BH_3 \cdot (CH_3)_2S$] in diethyl ether. Like DIBAH, diborane proved to be extremely efficient in the formation of **2c** without giving rise to the hydrogenolysis product **3c**. These results are even more remarkable when one considers that electron-withdrawing substituents should decrease electron density at the carbonyl group and, accordingly, decrease the rate with which boron (or aluminum) atom complexes with the carbonyl oxygen; thereby decreasing the rate of hydrogen transfer to carbon. Brown et al. have used this rationale in explaining their attempts to reduce chloral[18]. In a probe of the substituent effects on the reduction of α,α-dihaloketones with DIBAH and diborane, we carried out some comparative rate studies. At 10 °C, it was shown that **1a** reacted completely in less than 5 min in a two-fold excess of DIBAH in hexane while under the same conditions **1b** did not reduce until 45 min. Likewise, it was shown that **1b** was stable to BMS in ether for 10–15 h while **1a** reduced in less than 3 h. These data demonstrate that electronegative halogen substituents do slow the reduction of an adjacent carbonyl group. However, contrary to previous reports, the substituent effect did not prevent ultimate reduction. It is of interest to note that the work of Ioffe et al. substantiate our findings by demonstrating that chloral is reduced in a tetrahydrofuran solution of diborane[19]. Furthermore, our results dispute one additional point involving diborane reduction in tetrahydrofuran. Brown et al. have stated that diborane disproportionates in tetrahydrofuran to form small amounts of borohydride, according to: $2\,THF:BH_3 \rightleftarrows BH_4^{\ominus}(THF)_2BH_2^{\oplus}$. By this theory diborane reductions in tetrahydrofuran can then proceed by nucleophilic attack of borohydride anion rather than the expected electrophilic attack by borane[18]. Our data, however, strongly demonstrate that this is not the case, since the amount of hydrogenolysis during the reduction of the most labile α,α-dihaloketone **1c** would be proportional to the concentration of borohydride anion which is present for reaction. Thus, upon sodium borohydride reduction of **1c** a 50:50 mixture of mono- and dibromoalcohols formed, but B_2H_6/THF and $BH_3 \cdot (CH_3)_2S$/ether reductions afforded only the dibromoalcohol **2c**.

Both diborane and diisobutylaluminum hydride reductions have experimental advantages and disadvantages. DIBAH reductions in hexane were carried out at room temperature with a two-fold excess of reducing agent. Generally, this type of reduction was complete within 2 h and represented a much more rapid process than reductions involving BMS in refluxing ether[20]. Where solubility was a problem, benzene could be utilized as a co-solvent and, if additional temperature was desirable, heating could be applied up to 45 °C with DIBAH. However, unlike diborane reductions, DIBAH reaction work-up involved removal of gelatinous aluminum salts. Such salts can often trap the desired product and lessen the yield. Examples of reductions with DIBAH and diborane are shown below.

All isolated products were shown to be homogeneous by T.L.C. and/or G.L.C. analyses. Dihaloalcohols **2** or **5** found to be unstable to heat or light were converted to their acetate esters[12] prior to microanalysis.

1-(*o*-Chlorophenyl)-2,2-dichloro-1-propanone[14] **(1b)** and 1-(*o*-chlorophenyl)-2,2-dibromo-1-propanone[12] **(1c)** were prepared as described previously. 2,2-Dibromo-1-indanone[21] **(4a)**, 2,2-dibromo-1-tetralone[22] **(4b)**, and 2,2-dibromo-1-suberone[23] **(4c)** were prepared by literature methods.

1-(*o*-Chlorophenyl)-2-bromo-2-chloro-1-propanone (1d):
1-(*o*-Chlorophenyl)-2-chloro-1-propanone (18.3 g, 90 mmol) and *N*-bromosuccinimide (16.0 g, 90 mmol) are heated under reflux in carbon tetrachloride (200 ml) under illumination from a 300-W tungsten lamp. The reaction is complete after 6 h, when the orange color of the solution has disappeared. The solution is filtered, and the solvent evaporated. Spinning band distillation of the residue gives the product **1d**; yield: 21.0 g (84%); b.p. 80–85 °C/0.2 torr.

$C_9H_7BrCl_2O$	calc.	C 38.34	H 2.50	Br 28.34
(282.0)	found	38.65	2.76	28.70

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.48$ (s, 3H); 7.35 ppm (m, 4H).

I.R. (film): $\nu = 3080, 3000, 1720, 1590, 1220, 1050, 750\ cm^{-1}$.

Reduction of 1-(*o*-Chlorophenyl)-2,2-dibromo-1-propanone (1c) with Diisobutylaluminium Hydride (DIBAH); Typical Procedure:
To a stirred solution of **1c** (1.6 g, 5 mmol) under nitrogen in dry hexane (25 ml) is added fresh diisobutylaluminum hydride (10 ml, 20% in hexane) dropwise via a syringe. The solution is stirred at room temperature for 2 h and then cooled to 0 °C in an ice bath. Water (10 ml) is added, and the resulting white precipitate is filtered and washed with excess hexane. The combined hexane layers are washed with saturated sodium chloride solution and dried with sodium sulfate. Evaporation of the solvent affords *1-(o-chlorophenyl)-2,2-dibromo-1-propanol*[12] **(2c)** as a colorless liquid; yield: 1.5 g (90%); b.p. 120–126 °C/0.4 torr; m.p. of acetate[12]: 104–105 °C.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.20$ (s, 3H); 3.80 (d, 1H); 5.45 (d, 0.5H); 5.60 (d, 0.5H); 7.3 ppm (m, 4H).

I.R. (film): $\nu = 3500\ cm^{-1}$.

Table 1. Reduction of 1-(*o*-Chlorophenyl)-2,2-dihalo-1-propanones **1** (Scheme **A**)

Compound 1 No.	X	X	b.p. [°C]/ torr (Lit.)	Reagent	Solvent	Yield[a] [%] of **2**	b.p. [°C]/ torr (Lit.)	Yield[a] [%] of **3**	b.p. [°C]/ torr (Lit.)
1a	H	H	62-64°/0.35 (82-87°/1.5)[12]	$NaBH_4$	CH_3OH	85	90-92°/0.15[b]	0	—
				DIBAH	hexane	78		0	
				$BH_3:(H_3C)_2S$	ether	85		0	
1b	Cl	Cl	90°/0.8 (56-59°/0.75)[14]	$NaBH_4$	CH_3OH	89	79-81°/0.2 (79-81°/0.2)[14]	0	—
				DIBAH	hexane	86		0	
				$BH_3:(H_3C)_2S$	ether	95		0	
1c	Br	Br	126-132°/1.2 (115-118°/0.6)[12]	$NaBH_4$	CH_3OH	50	120-126°/0.4 (116-123°/0.3)[12]	50	106-115°/0.3 (105-108°/0.5)[12]
				$LiAl(OC_4H_9\text{-}t)_3H$	THF	55[c]		45[c]	
				$KB(C_4H_9\text{-}s)_3H$	ether	25[c]		75[c]	
				DIBAH	hexane	90		0	
				$BH_3:(H_3C)_2S$	ether	87		0	
				B_2H_6	THF	90		0	
1d	Cl	Br	80-85°/0.2[d]	$NaBH_4$	CH_3OH	40[c]	120-121°/0.1[d]	60[c]	—
				DIBAH	hexane	90		0	
				$BH_3:(H_3C)_2S$	ether	92		0	

[a] Yield of isolated product (not optimized) unless otherwise stated.

[b] $C_9H_{11}ClO$ (170.6) calc. C 63.34 H 6.49; found 63.49 6.52

[c] Yield by ^{1}H-N.M.R. spectroscopy.

[d] See experimental section.

Table 2. Reduction of Compounds **4a-c** (Scheme **B**)

Compound 4 No.	n	m.p. [°C] (Lit. m.p.)	Reagent	Solvent	Yield [%] of **5**	m.p. [°C] of **5** (solvent)	Molecular formula of **5**	Yield [%] of **6**
4a	1	130-132° [hexane] (133-134°)[21]	DIBAH	hexane/C_6H_6	81	52-54° (hexane)	$C_9H_8Br_2O$[a] (292.0)	0
			$BH_3:(H_3C)_2S$	ether	88			0
4b	2	56-59° [hexane] (59-60°)[22]	DIBAH	hexane/C_6H_6	84	61-63° (hexane)	$C_{10}H_{10}Br_2O$[b] (306.0)	0
			$BH_3:(H_3C)_2S$	ether	66			0
4c	3	43-44° [hexane] (42-44°)[23]	DIBAH	hexane/C_6H_6	55	oil	$C_{11}H_{12}Br_2O$ (320.0)[c]	0
			$BH_3:(H_3C)_2S$	ether	60			0

[a] Analysed as acetate.

[b] calc. C 39.25 H 3.29; found 39.26 3.33

[c] M.S.: $m/e = 320$ (M^+); 224 ($M^+ - HOBr$).

*1-(*o*-Chlorophenyl)-2-bromo-2-chloro-1-propanol* (**2d**) is obtained similarly from **1d**; yield: 90%; or by the BMS method (see below); yield: 92%; b.p. 120-121 °C/0.10 torr.

$C_9H_9BrCl_2O$	calc.	C 38.06	H 3.19
(284.0)	found	38.47	3.42

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.20$ (s, 3H); 3.80 (d, 1H); 5.45 (d, 0.5H); 5.60 (d, 0.5H); 7.3 ppm (m, 4H).

Reduction of 2,2-Dibromo-1-indanone (4a) with Borane:Dimethyl Sulfide (BMS); Typical Procedure:

To a stirred solution of **4a** (2.9 g, 10 mmol) in anhydrous ether (25 ml) is added BMS (2.5 ml of a 10 molar solution). The solution is refluxed for 24 h before cooling to room temperature. Ice-cold methanol (15 ml) is slowly added and stirring is continued for 2 h. Evaporation of the solvent and recrystallization of the residue from hexane affords *2,2-dibromo-1-indanol* (**5a**); yield: 2.6 g (88%); m.p. 52-54 °C; m.p. of acetate[12]: 78-80 °C (from hexane).

$C_{11}H_{10}Br_2O_2$	calc.	C 39.55	H 3.01
(334.0)	found	39.60	3.11

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.80$ (m, 3H); 5.10 (d, 1H); 7.25 ppm (m, 4H).

I.R. (film): $\nu = 3420$ cm^{-1}.

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