Kishner Eliminative Reduction of α-Halo Ketones[1]

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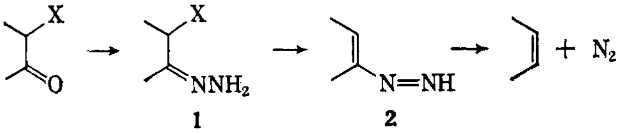
A reasonable reaction path for Kishner eliminative reduction of α-substituted ketones to olefins[2] involves hydrazone formation (→ **1**), internal elimination of the α-substituent (**1** → **2**), and collapse of alkenyldiimide **2** to olefin and nitrogen.[3] The temperature at which Kishner eliminative reduction occurs depends on the ease of elimination of the α-substituent. For example, it can be inferred that normal α-alkoxy ketones need high temperatures (>150°) to effect their reduction.[2] α-Phenoxypinacolone[2], however, is reduced to 3,3-dimethylbutene at 90° and α,β-epoxy ketones[4] undergo Kishner eliminative reduction to allylic alcohols at room temperature under nonbasic conditions. By extrapolation, Kishner eliminative reduction of α-sulfonyloxy ketones also should proceed under mild conditions, and we contemplated this unknown reaction as potentially satisfying a need which had arisen in other work for converting an acyloin to an olefin under mild conditions. First, however, we considered Kishner eliminative reduction of the more readily available α-halo ketones.



A survey of the literature on the reaction of α-halo ketones with hydrazine surprisingly[5a] drew an almost complete blank, and the little that could be found was not encouraging. In an entirely different endeavor, Macbeth found no nitrogen evolution from the reaction of 1-chloropropanone with excess hydrazine hydrate in alcohol.[6] There is, of course, no lack of possible reactions which might suppress the occurrence of eliminative reduction,[5b] one of the most likely being illustrated by the reported conversion of phenacyl chloride to phenacylhydrazine.[7] However, detection of Kishner eliminative reduction by observation of nitrogen evolution suggested a simple exploratory plan and we used this method to examine the reaction of hydrazine with 2-chlorocyclohexanone, a lucky choice as later events showed.

2-Chlorocyclohexanone, as distinct from 1-chloropropanone, with a large excess of hydrazine hydrate in alcohol, gave a small *but definitely not zero* amount of nitrogen (6%). Modification of reaction conditions, using potassium acetate to buffer the system in all cases, raised the yield of nitrogen to 35% by using only two to three equivalents of hydrazine hydrate. Eventually, a 75% yield was obtained by adding two to three equivalents of 95% hydrazine to a boiling solution of α-halo ketone in dimethoxyethane.[8] The isolation of cyclohexene from the product established that Kishner eliminative reduction was actually occurring, but a definitive correlation of nitrogen and olefin yields was not possible because cyclohexene could not be extracted quantitatively from dimethoxyethane solution. The necessary data were, however, provided by the 2α-halocholestanone series (halogen = F, Cl, Br, and I), where reduction was most effectively accomplished by adding the α-halo ketone to a two-phase system of boiling cyclohexene[9] or cyclohexane and excess hydrazine hydrate containing potassium acetate.[10] The results of these experiments are given in Table I.[11] It is quite clear that the amounts of nitrogen evolved and 2-cholestene formed were the same, even for the α-iodo ketone which is the most susceptible to reductive displacement on halogen.[12] 2-Cholestene was isolated from the washed product by percolation of a hexane solution through a column of alumina. This simple separation from the residue of more polar products yielded by evaporation of the filtrate white crystals of 2-cholestene, $[\alpha]_D$ +64°, with melting points ranging from 70–73° to 72–74° (lit.[13] m.p. 74.5–75°, $[\alpha]_D$ +69°;

TABLE I

2α-Halocholestanone	% nitrogen	% 2-cholestene
F	75	71
Cl	67	68
Br	64	62
I	54	54

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[1] Grateful acknowledgment is made of financial support from the Petroleum Research Fund (grant 1116-A4) and Research Corporation (Frederick Gardner Cottrell grant).

[2] The scope of the reaction has been reviewed by N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3269, 3272 (1955).

[3] See D. J. Cram and J. S. Bradshaw, *ibid.*, **85**, 1108 (1963), for references and a study of the decomposition of alkyldiimides.

[4] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); *cf.* Huang-Minlon and Chung-Tungshun, *Tetrahedron Letters*, **No. 19**, 666 (1961).

[5] (a) Surprisingly, because of the voluminous literature related to the reaction of α-halo ketones with amines; (b) for references, see C. L. Stevens, P. Blumbergs, and M. Munk, *J. Org. Chem.*, **28**, 331 (1963).

[6] E. L. Hirst and A. K. Macbeth, *J. Chem. Soc.*, 904 (1922).

[7] M. Busch and W. Foerst, *J. prakt. Chem.*, **119**, 287 (1928).

[8] This variation in yield can perhaps be ascribed to nucleophile-promoted diversions *after* alkenyldiimide formation. Tautomerization of alkenyldiimide to α,β-unsaturated hydrazone is one possibility. Another possibility is the formation of α-substituted hydrazones, from which the α-substituent can no longer be eliminated, by conjugate addition of hydrazine, alcohol, or water to alkenyldiimide. See V. R. Mattox and E. C. Kendall, *J. Am. Chem. Soc.*, **72**, 2290 (1950), and C. Djerassi, *ibid.*, **71**, 1003 (1949).

[9] Cyclohexene was used as solvent to prevent reduction of olefinic product by diimide to saturated hydrocarbon. Diimide can arise from oxidation of hydrazine and, although air oxidation was avoided by flushing the apparatus with an inert gas, and displacement by hydrazine on the halogen of the α-halo ketone was shown not to occur, no disadvantage can be seen to using (at least in part) an olefinic solvent which can competitively absorb any diimide formed. See E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *ibid.*, **83**, 3725 (1961), for references to diimide reductions. Note that reduction of 2-cholestene by diimide is implied in the Kishner eliminative reduction of 2-acetoxy-3-cholestanone; cholestane was found to be the main product [see L. Ruzicka, Pl. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 727 (1944)].

[10] The success of this system may be related to protection of alkenyldiimide from nucleophiles (see ref. 8). Rapid hydrazone formation results from projection through the interface of the highly polar carbonyl group and α-halogen atom. Elimination of halide may occur also at the interface, but surely is followed by withdrawal of the nonpolar cholestenyldiimide into the hydrocarbon phase.

[11] Also reduced by this method and reported here for completeness was 2α-fluorodihydrotestosterone (generously supplied by Dr. R. E. Counsell, Searle) in 70% yield.

[12] See G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950); included is the example of reductive dehalogenation by collidine of 2α-iodo-3-cholestanone to 3-cholestanone.

[13] D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

m.p. 75°, $[\alpha]_D$ +65.5°, +67.4°). The olefin was characterized by quantitative hydrogenation (1.00 equivalent of hydrogen absorbed) and conversion to 2β,3α-dibromocholestane.

After the work described so far was completed, other potential olefin syntheses, starting from 1,2-diols,[14] seemed more promising and our investigation of the Kishner eliminative reduction was terminated with a cursory survey of the scope of the reaction, based on the determination of nitrogen evolution. Table II gives the results of treating a variety of α-halo and α-sulfonyloxy ketones in dimethoxyethane solution with two to three equivalents of 95% hydrazine. Yields were good only for the α-halo cyclohexanones, decreasing sharply in the vertical columns with decreasing electrophilicity of the ketones.[15] The horizontal order[16] parallels both the electrophilicities of α-halo ketones (F > Cl > Br) and the resistance to elimination of the α-substituent in competitive reactions.[17]

To sum up, Kishner eliminative reduction of α-halo and α-sulfonyloxy ketones has been observed for the first time. Yields were sufficiently high in the conversion of α-halocyclohexanones to cyclohexenes that, for this special case, Kishner eliminative reduction should be considered as a practical alternative to the established two-step sequence *via* α-halohydrins.[18,19] Poor yields were, however, obtained from α-sulfonyloxy ketones and most other α-halo ketones.

TABLE II

α-Substituted ketone	Temp., °C.	% nitrogen F	Cl	Br	OSO_2R
2-Methylcyclohexanone	85		69		
Cyclohexanone	RT	0	61	52	36[a]
	85	79	74	54	15[a]
Cyclopentanone	RT		*b*		
Butanone	85			30[c,d]	
Propanone	RT	0		26[c]	17[c,e]
	85	10[c]	40[c]	32[c]	10[c,e]
	160[f]	32[c]			
Acetophenone	85		10		
Cyclodecanone	RT				0[a]
	85				0[a]

[a] OTs. [b] 40% of an unanalyzed mixture of nitrogen and cyclopentene. [c] Based on the assumption that the gas evolved contained equal amounts of nitrogen and olefin. [d] V.p.c. of the evolved gas showed that it contained equal amounts of *cis*- and *trans*-2-butene. The mixture of 2-butenes was contaminated with methyl bromide, presumably arising from demethylation of solvent by hydrogen bromide and indicating that potassium acetate does not act very rapidly as a buffer. [e] OMes. [f] Boiling diglyme.

Experimental[20]

Materials.—Dimethoxyethane, diglyme, and cyclohexene were distilled from lithium aluminum hydride. Chloropropanone, 3-bromo-2-butanone (Eastman Kodak), 2-chlorocyclohexanone, and 2-chlorocyclopentanone (Aldrich) were distilled. Generously supplied were 2-fluorocyclohexanone (Dr. A. S. Kende, American Cyanamid) and the dimethyl ketal of 2α-fluorocholestanone (Professor E. V. Jensen). 2α-Fluorocholestanone, m.p. 173–174°, lit.[21] m.p. 173–174°, was obtained by hydrolysis of the ketal with a few drops of concentrated hydrochloric acid in aqueous tetrahydrofuran solution. Prepared according to the literature were fluoropropanone[22]; bromopropanone[23]; mesyloxypropanone[24]; 2-bromocyclohexanone[25]; 2-chloro-2-methylcyclohexanone[26]; 2α-chlorocholestanone,[27] m.p. 179–181°, $[\alpha]_D$ +52° (lit.[28] m.p. 182°, +54°); 2α-bromocholestanone,[29] m.p. 167–169°, $[\alpha]_D$ +43.5° (lit.[28] m.p. 169°, +42°); 2α-iodocholestanone,[12] m.p. 131.5–133° dec. (lit.[28] m.p. 127°).

2-Tosyloxycyclohexanone.[30]—A solution of 1.0 g. (4.4 mmoles) of 2-hydroxycyclohexanone dimer (Aldrich) and 3.0 g. (15.7 mmoles) of tosyl chloride in 10 ml. of pyridine was allowed to stand for 12 hr. at 5°. The solution was poured into iced hydrochloric acid, extracted with ether, and washed. Crystallization of the crude product from ether yielded 1.3 g. (55%) of product, m.p. 73–76°. Further crystallization from ether gave an analytical sample with m.p. 75–76°.

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.20; H, 6.01; S, 11.93. Found: C, 58.13; H, 6.02; S, 11.72.

2-Tosyloxycyclodecanone.[30]—A solution of 1.0 g. (5.9 mmoles) of 2-hydroxycyclodecanone (Aldrich) and 1.5 g. (7.9 mmoles) of tosyl chloride in 3 ml. of pyridine similarly yielded 0.9 g. (47%) of product, m.p. 82–85°. Further crystallization from ether yielded an analytical sample with m.p. 86–87°.

Anal. Calcd. for $C_{17}H_{24}O_4S$: C, 62.95; H, 7.46; S, 9.87. Found: C, 62.98; H, 7.40; S, 9.75.

Small Scale Reductions.—To a 25-ml. flask connected through a condenser to a gas-collection buret and containing a magnetic stirring bar, 3.0 ml. of solvent, 1.5 g. (15 mmoles) of potassium acetate, and 1 mmole of α-substituted ketone was added the appropriate amount of 95% hydrazine or hydrazine hydrate. Vigorous stirring was maintained until no more gas was evolved (*ca.* 5 to 10 min.). The amount of gas collected was measured at room temperature, corrected for vapor pressure, and reduced by the appropriate blank reading.

Exemplary Large Scale Reduction of 2-Chloro-2-methylcyclohexanone.—To a 3-l. three-necked flask fitted with a stirrer and attached to a gas-measuring device (wet test meter, Precision Scientific Co.) were added 810 ml. of dimethoxyethane, 40 g. (0.41 mole) of potassium acetate, and 60 g. (0.41 mole) of 2-chloro-2-methylcyclohexanone. To the mixture, which was stirred and heated to reflux, was added dropwise 23 g. (0.68 mole) of 95% hydrazine. After a short induction period (*ca.* 3 min.) gas was evolved rapidly. A sample of gas was collected after bubbling through the wet test meter. Mass spectrometry showed, by comparison with pure nitrogen, that the collected gas was nitrogen, purity 95%. When no more gas was evolved (total collected corresponded to a yield of 65% nitrogen) the yellow-orange solution was cooled. Water (2 l.) and 4 l. of methylbutane were added to extract the methylcyclohexene. The lower phase was extracted with two 250-ml. portions of methylbutane which were added to the upper phase and washed with 2 l. of water, 2 l. of dilute sodium hydroxide solution, and two 2-l. portions of water. After drying with magnesium sulfate, the solution was percolated through a column of *ca.* 500 g. of silica gel (Davison).[31] The column was washed with more methylbutane, and the combined filtrates were distilled to yield

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[14] See, for example, E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).

[15] See M. S. Newman in "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 237.

[16] At 85°. Note that fluoride is a sufficiently poor leaving group that Kishner eliminative reduction of α-fluoro ketones is not observed at room temperature.

[17] See A. Streitwieser, Jr., *Chem. Rev.*, **56**, 653 (1956).

[18] See J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

[19] Note that the ease of reduction of α-halohydrins by zinc follows the trend I > Br > Cl and that no α-fluorohydrins have been reduced to olefins.

[20] Melting points are corrected. A 4-dm. tube was used to measure optical rotations which were determined photoelectrically with a Rudolph Model 80 polarimeter.

[21] R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

[22] H. Kitano and K. Fukui, *Kogyo Kagaku Zasshi*, **59**, 395 (1956); *Chem. Abstr.*, **51**, 11282 (1957).

[23] P. A. Levene, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 88.

[24] F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

[25] J. Allinger and N. E. Allinger, *Tetrahedron*, **2**, 64 (1958).

[26] E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Syn.*, **37**, 8 (1957).

[27] B. Ellis and V. Petrow, *J. Chem. Soc.*, 3869 (1953).

[28] General reference: L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

[29] L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953). See E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962), for comment on the possibility of 5–15% contamination of this bromo ketone with cholestanone.

[30] Prepared by Dr. R. V. Coombs.

[31] This purification is not only simple and effective, but also desirable on the grounds of safety. Attempted distillation (oil bath at 120°) of the crude product from reduction of 2-chlorocyclohexanone resulted in a violent explosion after most of the cyclohexene had distilled.

15.85 g. (41%) of 1-methylcyclohexene, b.p. 109–109.5°, $n^{25}\text{D}$ 1.4509 (lit.[32] 109.5°, $n^{20}\text{D}$ 1.4505). Extraction of the olefin was not quantitative as shown in a blank experiment; authentic 1-methylcyclohexene (Aldrich, distilled), subjected to the same isolation procedure, was recovered in 70% yield.

Reduction of 2α-Bromocholestanone.—To a 100-ml. three-necked flask containing a magnetic stirrer and attached through a condenser to a gas buret were added 13 ml. (0.4 mole) of hydrazine hydrate, 2 g. (20 mmoles) of potassium acetate, and 10 ml. of cyclohexene. The flask was heated until the cyclohexene boiled, and a solution of 2.004 g. (4.3 mmoles) of 2α-bromocholestanone in 30 ml. of cyclohexene was added dropwise over 10 min. while maintaining stirring and boiling. Heating was continued for 30 min. The light yellow mixture was cooled, extracted with ether–water, dried, evaporated, dissolved in hexane, and percolated through a column of acid-washed alumina (Merck). Evaporation of the filtrate yielded 995 mg. (64%) of 2-cholestene, m.p. 72–74°, $[\alpha]\text{D}$ +64°. Recrystallization from ether–ethanol (2:1) gave white needles of 2-cholestene in 95% yield, m.p. 73–75°, $[\alpha]\text{D}$ +65°.

Poorer results were obtained if the reagents were all mixed before heating. Thus a mixture of 2.009 g. of 2α-bromocholestanone, 13 ml. of hydrazine hydrate, 2 g. of potassium acetate, and 13 ml. of cyclohexene heated to reflux yielded a darker reaction mixture and only 269 mg. (19%) of 2-cholestene, m.p. 72–74°.

$2\alpha,3\beta$-Dibromocholestane.—To a solution of 109 mg. (0.29 mmole) of 2-cholestene, m.p. 73–75°, in 2 ml. of ether was added dropwise a solution of bromine in acetic acid until a slight excess of bromine was present. Evaporation of solvent and crystallization of the residue from ether–ethanol gave 76 mg. (49%) of white plates of $2\alpha,3\beta$-dibromocholestane, m.p. 123–124°, lit.[28] m.p. 125°.

Hydrogenation of 2-Cholestene.—Microhydrogenation of 40.6 mg. (0.11 mmole) of 2-cholestene, m.p. 72–74°, in acetic acid using 10% palladium on carbon as catalyst, led to the slow (*ca.* 6 hr.) uptake of 1.00 equivalent of hydrogen. Work-up of the solution gave a light yellow residue which was dissolved in hexane and percolated through a short alumina column. Evaporation of the filtrate yielded 34 mg. (85%) of crude cholestane, m.p. 75–80°. The melting point was raised to 79–80°, lit.[28] m.p. 80°, by crystallization from ether–ethanol.

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[32] G. Egloff, "Physical Constants of Hydrocarbons," Vol. 2, Reinhold Publishing Corp., New York, N. Y., 1940, p. 326.

Tropone. Selenium Dioxide Oxidation of 1,3,5-Cycloheptatriene

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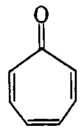
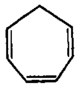
There are several methods known for the preparation of tropone (2,4,6-cycloheptatrien-1-one, I).[1–5] They range in scope from the degradation of tropinone[4] to produce I, to the formation of bis-2,4,6-cycloheptatrien-1-yl ether (III) from the hydrolysis of tropilium salts and subsequent disproportionation of the ether to give I and 1,3,5-cycloheptatriene (II).[2,3]



I



II

We have observed a direct oxidation of II by selenium dioxide in buffered aqueous dioxane to give I in about 25% yield. This reaction, though not high in yield, affords a simple one-step preparation of I from commercially available starting materials. The reaction can readily be adapted to large scale, and the inorganic product, selenium, can be recovered and reoxidized to selenium dioxide if desirable.[6]

Experimental

Preparation of Tropone.—To a solution of potassium dihydrogenphosphate (13.5 g., 0.1 mole) in water (33 ml.) was added 1,4-dioxane (330 ml.), 1,3,5-cycloheptatriene (43.0 g., 0.46 mole, Shell Chemical Corp., contained 6% toluene), and selenium dioxide (53.0 g., 0.48 mole, Matheson, Coleman and Bell). The mixture was warmed on the steam bath (90°) for 15 hr., allowed to cool to room temperature, and then filtered. The filtrate was poured into water (750 ml.) and extracted three times with 250-ml. portions of methylene chloride. The organic extract was washed with 10% sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to a dark brown liquid. Distillation of this liquid gave 12.8 g. (25%) of pale yellow tropone, b.p. 91–92° at 4 mm., $n^{23}\text{D}$ 1.6152. The infrared spectrum of this material was identical with that reported by Doering.[5]

Acknowledgment.—The author wishes to thank Shell Chemical Corporation for its generous supply of 1,3,5-cycloheptatriene.

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[1] J. Birch, M. Graves, and F. Stansfield, *Proc. Chem. Soc.*, 282 (1962).

[2] T. Nozoe, T. Ikemi, and H. Sugiyama, *Chem. Ind.* (London), 932 (1960).

[3] A. P. ter Borg, *Helv. Chim. Acta*, **43**, 457 (1960).

[4] J. Meinwald, S. Emerman, N. Yang, and G. Büchii, *J. Am. Chem. Soc.*, **77**, 4401 (1955).

[5] M. von E. Doering and F. Detert, *ibid.*, **73**, 877 (1951).

[6] N. Rabjon, "Organic Reactions," Coll. Vol. V, R. Adams, Ed., John Wiley and Sons, New York, N. Y., 1949, p. 345.

The Reaction of Chlorocarbene with Styrene

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A number of carbenes or "carbene-like" species have been added to styrene to give substituted phenylcyclopropanes.[1] Closs and co-workers[2] have generated chlorocarbene from methylene chloride and methyl- or *n*-butyllithium and added it to various olefins to give substituted chlorocyclopropanes. The work which is now reported was undertaken to study the addition of chlorocarbene to styrene.

When ethereal *n*-butyllithium, prepared from *n*-butyl bromide and lithium, was allowed to react with methylene chloride in the presence of excess styrene, two stereoisomeric 1-chloro-2-phenylcyclopropanes were isolated in low yields in addition to several gaseous products. The yields of **1** (4.1%) and **2** (4.9%) are based on distilled material, assuming equal thermal conductivities on gas chromatographic (g.c.) analysis. The structural

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[1] (a) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956); (b) W. J. Dale and P. E. Swartzentruber, *J. Org. Chem.*, **24**, 955 (1959); (c) A. Nagasaka and R. Oda, *Kogyo Kagaku Zasshi*, **59**, 1024 (1956); (d) H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4990 (1961); (e) A. Burger and W. L. Yost, *ibid.*, **70**, 2198 (1948); (f) R. J. Mohrbacher and N. H. Cromwell, *ibid.*, **79**, 401 (1957); (g) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959); (h) G. Wittig and K. Schwarzenbach, *Ann.*, **650**, 1 (1961).

[2] G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960), and subsequent papers.