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REDUCTION OF α-HALOKETONES WITH LITHIUM IODIDE AND BORON TRIFLUORIDE

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Treatment of α-bromoketones with lithium iodide and boron trifluoride in ether or tetrahydrofuran at room temperature affords the parent ketone in a procedure which compares favorably in terms of yield, mildness of reaction conditions, and experimental convenience with any of the numerous known methods for this type of reduction (1, 2). The yields of dehalogenated ketones listed in Table I are of isolated, sublimed or recrystallized, product. Analysis by tlc or vpc of the crude product from α-bromoketones showed the parent ketone as the only product in all but one case. The one exception, in which a trace of unreacted starting material remained, was α-bromocamphor, for which analogous dehalogenation with triphenylphosphine has been reported to fail (2).

The following is a typical experiment. A solution of 0.807 g (3.00 mmol) of 2-bromo-2-methyl-5-methoxy-1-tetralone (I) and 0.46 ml (3.7 mmol) of boron trifluoride etherate in 30 ml of anhydrous ether was added dropwise over 45 min to a solution of 1.34 g (10 mmol) of lithium iodide (Alfa Inorganics, "anhydrous") (3) in 30 ml of ether under nitrogen (4) at room temperature. The mixture was stirred magnetically during the addition and until the reaction was complete (as indicated by tlc) (5). Dilute sodium thiosulfate solution (15 ml) was added to discharge the dark brown color of triiodide ion formed during the reaction (6). The colorless ether layer was separated, washed well with water to remove iodide ion, dried, and evaporated. Vacuum sublimation of the residue yielded 0.550 g (97%) of pure 2-methyl-5-methoxy-1-tetralone (II).

Table I

Reduction of α-Haloketones with Lithium Iodide and Boron Trifluoride Etherate[a]

	% Yield of Parent Ketone	
α-Haloketone Reduced	Estimated	Purified Product
2-Bromo-2-methyl-5-methoxy-1-tetralone (I)[b]	100[c]	97
2-Bromo-5-methoxy-1-tetralone (III)	100[c]	98
2-Iodo-5-methoxy-1-tetralone (IV)[b]	100[c]	
2-Bromocyclohexanone	100[d]	
2-Bromocyclododecanone	100[c]	
p-Bromophenacyl bromide	100[c]	98.5
2α-Bromocholestanone[e]	100[c]	96
2α, 4α-Dibromocholestanone[e]	100[c]	93
α-Bromocamphor	95[c,d]	85
Phenacyl chloride	100[c]	
2-Chlorocyclopentanone	100[d]	
α-Chloronorbornanone (VI)	0[d]	

[a] Conditions as described in the text except as noted.

[b] Compounds I, mp 76-77°, and IV, mp 121-122°, have not been previously reported. Elemental analyses and spectral properties consistent with the structural assignments were obtained.

[c] By tlc analysis

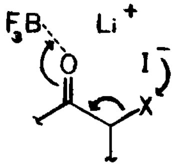
[d] By vpc analysis

[e] Added as benzene solutions containing boron trifluoride etherate to ethereal solutions of lithium iodide.

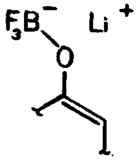
That the specified combination of reagents is necessary for reduction is demonstrated by the following facts. 2-Bromo-5-methoxy-1-tetralone (III) is unchanged by treatment with BF_3 in ether for 24 hr; it is converted to 2-iodo-5-methoxy-1-tetralone (IV) essentially quantitatively by lithium iodide in ether within 24 hr. Treatment of IV with BF_3 in ether likewise affords no reaction for 17 hr, but upon addition of excess lithium iodide to this mixture, conversion to 5-methoxy-1-tetralone (V) is complete within one minute.

The procedure is also effective for reduction of α-chloroketones (such as phenacyl chloride and 2-chlorocyclopentanone) in which the chlorine can be nucleophilically displaced by iodide ion, but fails completely with the hindered α-chloronorbornanone (VI) (quantitative recovery of VI after 24-hr reflux of the usual reaction mixture).

The hypothesis which led to the use of the LiI-BF_3 combination, and which is consistent with all the facts cited above, was that the Lewis acid might facilitate nucleophilic attack at halogen by coordinating with the carbonyl group and making the organic substrate a better leaving group, as illustrated in VII → VIII. However, experiments designed to trap the conjectured enol fluoroborate (VIII) with subsequently added electrophiles, including deuterium oxide, initially failed. The source of the hydrogen which was becoming attached to the α-carbon during the course of the reaction was determined not to be the ethereal medium by appropriate experiments in tetrahydrofuran-d_8. The hydrogen was eventually found to originate, presumably as water, in even relatively carefully dried lithium iodide (7), for when the lithium iodide was generated <u>in situ</u> by the reaction of lithium hydride with iodine (8), **substantial** formation of α-deuterioketone (II-2d) occurred during deuterium oxide workup (9). Efforts continue to effect reaction of other electrophiles at the α-carbon of the proposed lithium enol fluoroborate intermediates.



VII



VIII

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References

(1) *e.g.*: (a) E.J. Corey and G.A. Gregoriou, *J. Amer. Chem. Soc.*, **81**, 3127 (1959); (b) G. Stork and F.H. Clarke, *ibid.*, **83**, 3114 (1961); (c) R.E. Lutz, *et al.*, *ibid.*, **68**, 1813 (1946); (d) G.A. Fleisher and E.C. Kendall, *J. Org. Chem.*, **16**, 573 (1951); (e) P.L. Julian, *et al.*, *J. Amer. Chem. Soc.*, **67**, 1728 (1945); (f) K.L. Williamson and W.S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961); (g) T. Goto and Y. Kishi, *Chem. Abstr.*, **58**, 14059a (1963); (h) H.G. Kuivila and L.W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963); (i) I.J. Borowitz, K.C. Kirby, Jr., P.E. Rusek, and E. Lord, *ibid.*, **34**, 2687 (1969).

(2) I.J. Borowitz, P.E. Rusek, and R. Virkhaus, *ibid.*, **34**, 1595 (1969), and references therein.

(3) Deliberate addition of several equivalents of water, or use of obviously wet lithium iodide, results in slower and incomplete reduction.

(4) The reduction can in many cases be effected quantitatively and instantaneously simply by mixing the reagents in an open test tube without any precautions; the procedure given works in all cases.

(5) This requires one minute to several hours depending on the substrate and exact reaction conditions.

(6) Analysis by titration with thiosulfate indicated formation of 1 ± 5% equivalent of iodine.

(7) The lithium iodide was typically heated *in vacuo* at 110° for 5-10 hr.

(8) M.D. Taylor and L.R. Grant, *J. Amer. Chem. Soc.*, **77**, 1507 (1955); H.O. House and W.F. Fischer, Jr., *J, Org. Chem.*, **33**, 949 (1968).

(9) Solid sodium carbonate was added to the reaction mixture before workup in these labeling experiments because this was found in control experiments to prevent isotopic exchange of II in D_2O and II-2d in H_2O.