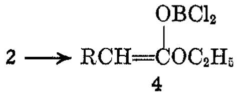
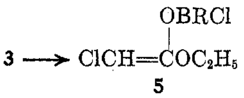
Pasto and Wojtkowski[10] have recently isolated several enol borinates and suggest that intermediates such as **2** or **3** exist in the isomeric enol borinate forms **4** or **5**. Thus, if this reaction involves an α bora ester, the boron must migrate to oxygen (eq 5 and 6). Such intermediates are rapidly hydrolyzed by water.



$$2 \longrightarrow \underset{\mathbf{4}}{\mathrm{RCH{=}\overset{OBCl_2}{\overset{|}{C}}OC_2H_5}} \qquad (5)$$



$$3 \longrightarrow \underset{\mathbf{5}}{\mathrm{ClCH{=}\overset{OBRCl}{\overset{|}{C}}OC_2H_5}} \qquad (6)$$

Since α-haloboranes rearrange upon addition of a nucleophile,[11] methanolysis of **2** or **3** should give alkyl homologated esters unless protonolysis competes with the rearrangement. In an attempt to increase the yield of alkyl homologation, nucleophiles such as pyridine and triethylamine were added. After transfer, protonolysis should then give the alkyl ester. However, the yields of alkyl ester did not improve, suggesting that the rearrangement to the enol borinates **4** and **5** may be fast and irreversible even at $-62°$. Alternatively, the α transfer must be slow at these temperatures even when catalyzed by good nucleophiles. Attempts to identify definitively the intermediates by nmr were unsuccessful owing to the complicated spectrum of the mixture.

If the reasonable assumption is made that the conversion to the enol borinate is faster than rearrangement, the yields of chloro, alkyl, and aryl esters indicate their relative migratory aptitude. The data in Table I thus suggests the migratory aptitude to be in the order $\mathrm{Ar} > \mathrm{R} > \mathrm{Cl}$. Such an order for aryl *vs.* alkyl has previously been observed in the rearrangements of α-haloboronates.[12]

In spite of some limitations, this reaction provides a highly useful and operationally simple method for converting alkenes/arenes to their corresponding two-carbon chain-lengthened ethyl esters. Simple procedures have recently become available for the synthesis of the required alkyldichloroboranes[6] and aryldichloroboranes.[7]

We are continuing to explore the use of alkyl and aryldichloroboranes in organic synthesis.

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[10] D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

[11] H. C. Brown and Y. Yamamoto, *J. Amer. Chem. Soc.*, **93**, 2796 (1971).

[12] D. S. Matteson and R. W. H. Mah, *J. Amer. Chem. Soc.*, **85**, 2599 (1963).

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RECEIVED MARCH 20, 1973

α-Halocarbonyl Compounds. II. A Position-Specific Preparation of α-Bromo Ketones by Bromination of Lithium Enolates. A Position-Specific Introduction of α,β-Unsaturation into Unsymmetrical Ketones

Summary: Low-temperature bromination of specifically generated ketone enolates under aprotic conditions produces position-specific α-bromo ketones which can be converted to α,β-unsaturated ketones; no Favorskii rearrangement or other base-catalyzed side reactions and no positional equilibration of bromine are observed.

Sir: Because α-halocarbonyl compounds are useful synthetic intermediates in a number of widely different organic transformations,[1] we have been interested for some time in devising some new efficient methods for their preparation.[2] Common methods for preparing α-halo ketones, in general, provide little position selectivity if both α and α' positions are available for direct halogenation.[1a,3a] The available, generally applicable methods[3] for specific preparation of either α- or α'-halogenated unsymmetrical ketones usually require extensive reaction sequences or produce the desired product in only moderate yield, often still contaminated with significant amounts of isomeric halo ketone. Even the well-known bromination of isomerically specific, neutral enol derivatives[3c,d] of unsymmetrical ketones, *e.g.*, enol acetates, suffers the disadvantage that acidic by-products may catalyze equilibration of starting material or of product halo ketone. Consequently, both α- and α'-bromo ketones, as well as polybrominated materials, may be observed.

Perhaps the most obvious method for position-specific halogenation of unsymmetrical ketones, the quenching of position-specific enolate anions[4] by halogen, has not received appropriate attention because of the attendant possibility of subsequent reactions (Favorskii rearrangements and/or alkylations and condensations) of the often quite reactive α-halo ketones under strongly basic reaction conditions. However, we wish to report that bromination of lithium enolates at low temperature is as effective a method for preparing specifically α- or α'-

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[1] See a–d for examples. (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., pp 459–478. (b) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **90**, 6218 (1968); **91**, 2147 (1969); **91**, 6852 (1969). (c) T. A. Spencer, R. W. Britton, and D. S. Watt, *ibid.*, **89**, 5727 (1967). (d) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. Fr.*, 366 (1958).

[2] (a) P. L. Stotter and K. A. Hill, "γ-Halotiglates: Ubiquitous Reagents for Natural Products Synthesis," paper delivered before the Second International Symposium on Synthesis in Organic Chemistry, Cambridge, England, July 1971. (b) P. L. Stotter and K. A. Hill, *Tetrahedron Lett.*, 4067 (1972).

[3] (a) Other halogenation methods (direct and indirect) which may, *in certain cases*, provide positional selectivity are also reviewed in ref 1a. (b) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5415 (1955). (c) H. Piotrowska, W. Wojnarowski, B. Waegell, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 3511 (1965). (d) We have observed that direct bromination of the less substituted enol silyl ether derived from 2-methylcyclohexanone gives a complex product mixture at $-20°$; more promising results were obtained at $-70°$, but some difficulties were nonetheless encountered in our attempts to separate product bromo ketone from trimethylsilanol and hexamethyldisiloxane on work-up.

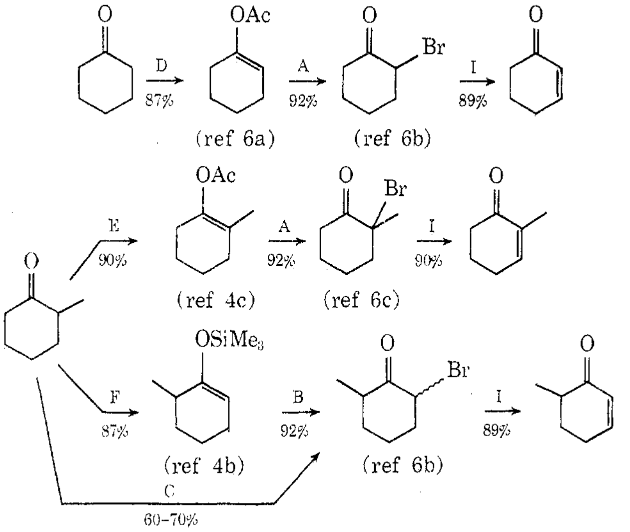
[4] (a) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965), and references cited therein. (b) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90**, 4462, 4464 (1968); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969). (c) H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

bromo ketones, as has already been reported for preparing the more readily available α-bromo esters.[2a,5]

Position-specific lithium enolates generated in tetrahydrofuran from enol acetates,[4a] enol silyl ethers,[4b] or directly from the ketone (by the kinetic action of lithium diisopropylamide[4c]) were brominated at −78° by rapid addition of 1 equiv of bromine, as a solution in methylene chloride. This cold reaction, which instantaneously decolorized the bromine solution, was stirred for 1 min and then rapidly quenched with excess aqueous sodium bicarbonate. Extraction of the resulting slurry with pentane allowed isolation of the desired α-bromo ketone in good to excellent yield. The crude bromo ketones showed negligible amounts of polybromination or equilibration of bromine to the α′ position. We observed no evidence of Favorskii rearrangement or of alkylation or condensation by-products, even in those cases where stronger base than lithium enolate was present (enolate solutions derived from enol acetates by the action of methyllithium contained 1 equiv of lithium *tert*-butoxide). Some representative results for the direct bromination of lithium enolates are described for several unsymmetrical ketones in Schemes I and II.[6]

SCHEME I[a]

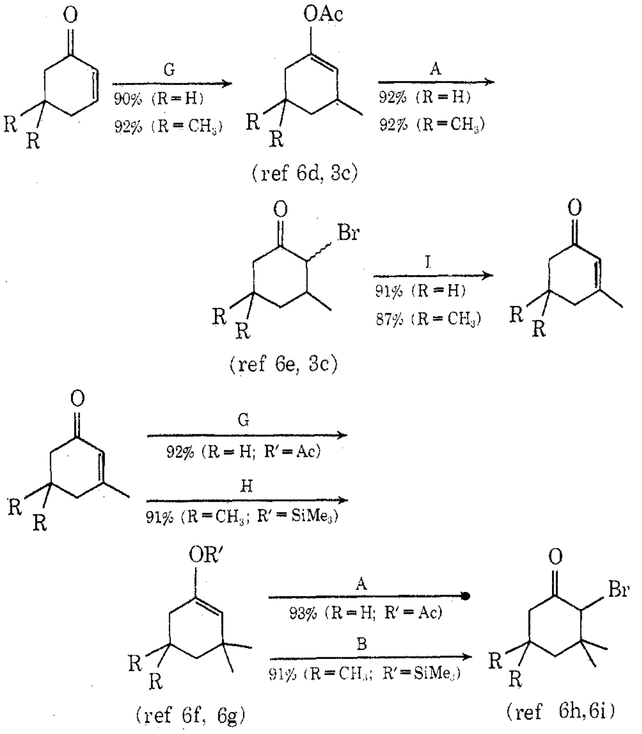
BROMINATION OF ENOLATES DERIVED FROM CYCLOHEXANONE AND 2-METHYLCYCLOHEXANONE



[a] Procedures for generation of lithium enolates and subsequent bromination: (A) enol acetate and 2 equiv of MeLi in THF at room temperature, addition Br$_2$ in CH$_2$Cl$_2$ at −78°, quench with aqueous bicarbonate;[4a] (B) enol silyl ether and 1 equiv of MeLi in THF at room temperature, addition Br$_2$ in CH$_2$Cl$_2$ at −78°, quench with aqueous bicarbonate;[4b] (C) ketone and 1 equiv of lithium diisopropylamide in THF at room temperature, addition Br$_2$ in CH$_2$Cl$_2$ at −78°, quench with aqueous bicarbonate, final work-up with cold dilute sulfuric acid[4c] (product may contain small amounts of α′-brominated isomer depending on contact time with acid). Procedures for preparation of enol derivatives: (D) mixture of ketone, isopropenyl acetate, and catalytic TsOH with distillation of acetone;[6a] (E) mixture of ketone, Ac$_2$O, and catalytic HClO$_4$ in CCl$_4$ at room temperature;[4c] (F) ketone and 1 equiv of lithium diisopropylamide in THF at room temperature, quench at 0° with excess ClSiMe$_3$ and Et$_3$N, bicarbonate then dilute acid work-up; (G) unsaturated ketone and 1.1 equiv of LiMe$_2$Cu in ether at 0°, quench with excess Ac$_2$O, partition between aqueous bicarbonate and pentane with cold dilute ammonium hydroxide work-up; (H) unsaturated ketone and 1.1 equiv of LiMe$_2$Cu in ether at 0°, quench with excess ClSiMe$_3$ and Et$_3$N, partition between aqueous bicarbonate and pentane with cold dilute acid work-up. Procedure for dehydrobromination: (I) crude α-bromo ketone in DMF added dropwise to excess Li$_2$CO$_3$ and LiBr in DMF at ~130°.[1d]

SCHEME II[a]

BROMINATION OF ENOLATES DERIVED FROM TRAPPED INTERMEDIATES OF CONJUGATE ADDITION TO CYCLOHEXENONES



[a] See Scheme I, footnote *a*.

Note that the yields of α-bromo ketone are extremely high[6] in all cases where no reactive amine is present. Even when a secondary amide base was used to generate the kinetic enolate of 2-methylcyclohexanone and the subsequent bromination carried out in the presence of secondary amine, the yield of α-bromo ketone is superior to those observed with most other methods of preparation. And, finally, the purity of α-bromo ketones prepared by enolate bromination as directly derived from evaporation of the pentane extract is sufficient for use in most synthetic transformations requiring these versatile intermediates.

The enol derivatives[6] used as precursors to α-bromo ketones in Scheme II were derived in high yield by conjugate addition of 1.1 equiv of lithium dimethylcopper in ether at 0° to the appropriate α,β-unsaturated

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(5) M. W. Rathke and A. Lindert, *Tetrahedron Lett.*, 3995 (1971).

(6) Yields indicated in Schemes I and II for enol acetates, enol silyl ethers, and enones represent distilled materials in each case. Yields indicated for α-bromo ketones were carefully estimated by nmr examination of samples directly obtained by reduced pressure evaporation of the pentane extracts. Further purification (*e.g.*, distillation or chromatography) often resulted in positional equilibration of bromine as well as destruction of extensive amounts of the unstable bromo ketones. That this method of estimating yields is reasonably accurate was demonstrated by the high-yield conversion of several of these crude α-bromo ketones to known α,β-unsaturated ketones as described in the text. All α-bromo ketones and their precursors were identified by comparison with known samples or by careful correlation of observed spectral data and physical constants with those already reported (see references cited in Schemes I and II): (a) H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949); (b) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965); (c) W. W. Rinne, H. R. Deutsch, M. I. Bowman, and I. B. Joffe, *J. Amer. Chem. Soc.*, **72**, 5759 (1950); (d) L. Bardou, J. Elquero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 297 (1967); (e) C. Djerassi, L. E. Geller, and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960); (f) J. Champagne, H. Favre, D. Vocelle, and I. Zbikowski, *Can. J. Chem.*, **42**, 212 (1964); (g) P. F. Hudrlik, Ph.D. Thesis, Columbia University, New York, N. Y., 1968; (h) H. Duerr, G. Ourisson, and B. Waegell, *Chem. Ber.*, **98**, 1858 (1965); (i) B. Waegell, *Bull. Soc. Chim. Fr.*, 855 (1964).

ketone; the resultant enolate mixtures were trapped[7] by addition of excess acetic anhydride or of chlorotrimethylsilane (mixed with triethylamine).

Finally, it should also be noted that this position-specific α bromination of unsymmetrical ketones readily allows the introduction of specific α,β unsaturation *via* direct dehydrobromination[1d] of the crude α-bromo ketone. Accordingly, in 70–75% overall yield, 2-methylcyclohexanone was converted specifically to either methylcyclohexenone shown in Scheme I. Scheme II further demonstrates that similar dehydrobromination of α-bromo ketones derived from conjugate addition completes, in comparable overall yield, a sequence which is, formally, the nucleophilic substitution of alkyl for hydrogen at the β position of α,β-unsaturated ketones. A forthcoming publication will describe in greater detail this β-nucleophilic substitution sequence.

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[7] (a) For reports of enol silyl ethers by quenching magnesium enolates (from copper-catalyzed Grignard conjugate additions), see ref 4b and 6g. (b) For reports of enol acetates by quenching magnesium enolates using acetyl chloride, see J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969). (c) For a preliminary report of enol acetates by quenching complex lithium–copper enolates (from lithium dialkylcopper conjugate additions) with acetyl chloride, see E. Piers, W. de Waal, and R. W. Britton, *ibid.*, **93**, 5113 (1971).

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