Reductive Acylation of Ketones. II [1,2]

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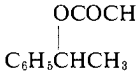
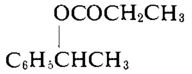
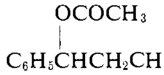
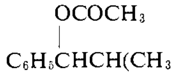
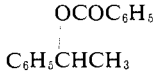
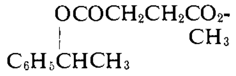
Abstract: Some ketone-to-ester conversions brought about in high yield under neutral and mild conditions are described. The reaction involves treatment of the ketone with an acid chloride and triphenyltin hydride and results in reductive acylation of the ketone.

As the start of a program designed to develop synthetic methods for the addition of the elements of R–H across unsaturated linkages, we recently reported some examples of the addition of RCO–H across ketone carbonyl groups.[2] These ketone-to-ester conversions involved the reaction of an acid chloride with triphenyltin hydride in the presence of a ketone and resulted in "quantitative" conversion of the ketone to the desired ester. However, the method, as described, was not generally applicable, since the examples reported concerned only ketones of the type PhCOR. It is the purpose of this paper to give a more detailed account of this work and to present some applications of the reaction to dialkyl ketones. An account of previous work has already been given.[2,3]

Discussion of Results

The reaction system consisted of acid chloride, triphenyltin hydride, and ketone in benzene as solvent. In all cases, listed in Table I, "quantitative" conversions of the ketone to the desired ester were obtained, except in that procedure leading to isopropyl benzoate, in which the conversion was 90%. In these systems, we have observed the following reactions: (A) reaction of all three reagents to yield the desired ester, (B) reduction of the acid chloride to aldehyde by triphenyltin hydride, (C) reaction between the ketone and triphenyltin hydride, (D) reaction between the ketone and acid chloride. The relative rates of these reactions vary significantly from system to system. However, in each case, it is possible to choose reaction conditions such that reaction A predominates overwhelmingly. Examples of each type of procedure are given in the Experimental Section.

Table I. Summary of Systems Studied

Reactants[a]	Product	Procedure[b]
CH_3COCl, $C_6H_5COCH_3$	 $C_6H_5\overset{\overset{OCOCH_3}{\vert}}{C}HCH_3$	I
CH_3CH_2COCl, $C_6H_5COCH_3$	 $C_6H_5\overset{\overset{OCOCH_2CH_3}{\vert}}{C}HCH_3$	I
CH_3COCl, $C_6H_5COCH_2CH_3$	 $C_6H_5\overset{\overset{OCOCH_3}{\vert}}{C}HCH_2CH_3$	I
CH_3COCl, $C_6H_5COCH(CH_3)_2$	 $C_6H_5\overset{\overset{OCOCH_3}{\vert}}{C}HCH(CH_3)_2$	I
C_6H_5COCl, $C_6H_5COCH_3$	 $C_6H_5\overset{\overset{OCOC_6H_5}{\vert}}{C}HCH_3$	I, at 122°
CH_3COCl, $CH_3CH_2COCH_2CH_3$	$(CH_3CH_2)_2CHOCOCH_3$	I
$CH_3O_2CH_2CH_2COCl$, $C_6H_5COCH_3$	 $C_6H_5\overset{\overset{OCOCH_2CH_2CO_2CH_3}{\vert}}{C}HCH_3$	I
CH_3COCl, CH_3COCH_3	$(CH_3)_2CHOCOCH_3$	II
C_6H_5COCl, CH_3COCH_3	$(CH_3)_2CHOCOC_6H_5$	III

[a] In addition to triphenyltin hydride and the solvent benzene. [b] See the Experimental Section for examples of each type of procedure.

Experimental Section

In all cases yields were determined by use of nmr spectroscopy and gas chromatographic analysis.

Materials. Acetyl chloride, acetophenone, α-phenethyl acetate, propionyl chloride, propiophenone, isobutyrophenone, benzoyl chloride, 3-pentanone, 3-carbomethoxypropionyl chloride, acetone, isopropyl acetate, isopropyl benzoate, and benzene were commercial materials and were used without further purification. Triphenyltin hydride[6] (stored under nitrogen in a refrigerator), α-phenethyl benzoate,[7] and α-phenethyl propionate[8] were prepared by literature procedures. 3-Pentyl acetate was prepared by a procedure reported for *t*-butyl acetate.[9] α-Phenylpropyl acetate and α-isopropylbenzyl acetate were prepared by a procedure reported for β-phenylpropyl acetate.[10]

α-Phenethyl 3-carbomethoxypropionate, bp 123–124.5° (1.0–0.9 mm), the only previously unreported compound used in this work, was prepared by reaction of 3-carbomethoxypropionyl chloride with α-methylbenzyl alcohol and pyridine. Its nmr spectrum showed no unusual features.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.39; H, 7.13.

Procedure I. Preparation of α-Phenethyl Acetate. Acetyl chloride (0.0311 g, 0.396 mmole), 0.0492 g (0.410 mmole) of acetophenone, and 0.1482 g (0.528 mmole[11]) of triphenyltin hydride were allowed to stand in 0.148 g of benzene for 0.5 hr at room

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[1] This work was supported by American Cancer Society Institutional Grant 41-F and National Institutes of Health Grant GM-13662-01.

[2] Part I: L. Kaplan, *J. Am. Chem. Soc.*, **88**, 1833 (1966).

[3] After the original communication[2] was submitted, papers appeared by Kuivila[4] and Kupchik[5] on the reaction between acid chlorides and tin hydrides. Some examples of the addition of acyl radicals to added ketones were noted in the former paper. However, the experimental conditions and tin hydride chosen were such that conversions to mixed ester of 5, 12, and 3% were obtained in the three examples given.

[4] H. G. Kuivila and E. J. Walsh, Jr., *J. Am. Chem. Soc.*, **88**, 571, 576 (1966).

[5] E. J. Kupchik and R. J. Kiesel, *J. Org. Chem.*, **31**, 456 (1966).

[6] H. G. Kuivila and O. F. Beumel Jr., *J. Am. Chem. Soc.*, **83**, 1246 (1961).

[7] R. Huisgen and C. Rüchardt, *Ann.*, **601**, 21 (1956).

[8] Sh. Mamedov, D. N. Khydyrov, and Z. Seid-Rzaeva, *Zh. Obshch. Khim.*, **33**, 1171 (1963).

[9] A. Spassow, *Org. Syn.*, **20**, 21 (1940).

[10] C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, **77**, 369 (1955).

[11] It was not determined whether this large an excess was necessary for "quantitative" conversion.

temperature. "Quantitative" conversion of the acetophenone to α-phenethyl acetate was obtained.

Procedure II. Preparation of Isopropyl Acetate. (This procedure was used when reaction D was the predominant reaction using procedure I.) Acetyl chloride (0.78 ml, 11.0 mmoles) in 4 ml of benzene was added dropwise at room temperature to a solution of 0.62 ml (8.5 mmoles) of acetone and 3.6 ml (16.6 mmoles[11]) of triphenyltin hydride in 4 ml of benzene over a period of 33 hr. "Quantitative" conversion of the acetone to isopropyl acetate was obtained.

Procedure III. Preparation of Isopropyl Benzoate. (This procedure was used when reactions B and C were predominant using procedure I.) Triphenyltin hydride (1.8 ml, 8.3 mmoles[11]) in 2 ml of benzene was added dropwise to a refluxing (91° bath temperature) solution of 0.31 ml (4.3 mmoles) of acetone and 0.75 ml (6.5 mmoles[11]) of benzoyl chloride in 2 ml of benzene over a period of 14 min. The reaction mixture was then refluxed for an additional 14 min; 90% conversion of the acetone to isopropyl benzoate was obtained.

Acknowledgments. We are grateful to M and T Chemicals for a gift of triphenyltin chloride and to the National Science Foundation for funds for the purchase of a Varian A-60 nmr spectrometer.

The Structure of the Cyclopropylmethyl Carbonium Ion

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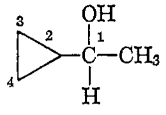
Abstract: The stereochemical consequence of formation and reaction of the cyclopropylmethyl carbonium ion was investigated by comparing the rate of acid-catalyzed racemization of optically active cyclopropylmethylcarbinol (**1**) with the rate of replacement of the hydroxyl group. It was observed that $k_{\text{rac}} \sim k_{\text{ex}}$. The implications of this finding for the structure of the cyclopropylmethyl carbonium ion are discussed.

A variety of experiments indicate that the cyclopropyl group is remarkably more effective than other alkyl groups in stabilizing carbonium ions.[2,3] In fact, stabilization by cyclopropyl is even greater than by phenyl. This stabilization must be due, of course, to extensive delocalization of positive charge into the cyclopropyl rings, and a number of representations have been proposed for this delocalization.[2]

This study of the stereochemistry of product formation from the carbonium ion generated from optically active cyclopropylmethylcarbinol (**1**) in aqueous acid provides evidence relating to the geometric requirement for maximum conjugation in cyclopropyl carbonium ions. Attention is focused particularly on the dihedral angle around the cyclopropyl-C$^+$ bond. The reaction chosen was the replacement of H_2O by H_2O^{18}. The stereochemistry of this substitution can be inferred from comparison of the rate of this exchange (k_{ex}) with the rate of racemization (k_{rac}).



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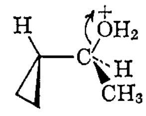

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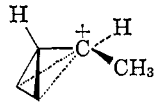
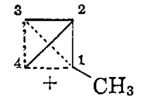


3

If, for example, the ion had the "crown" geometry[3,4] depicted in **3** (the dotted lines are intended to clarify the geometry, not to indicate the nature of the bonding), optically active products might be expected since **3** itself is active. Substitution with predominant retention of configuration would be reasonable; probably departure of water from the protonated alcohol (**2**) would lead to **3** (rather than to the enantiomer of **3**) and addition of water would give back **2**. Of the structures that have been proposed to represent the delocalization of charge in cyclopropyl carbonium ions, the tricyclobutonium ion structure (**4**),[5,6] which postulates direct bonding of C-1 to C-3 and C-4, would be expected to have the crown geometry. A distorted crown geometry would be predicted for the bicyclobutonium ion structure (**5**), which involves direct bonding of C-1 to C-4.[6,7]



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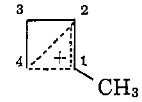

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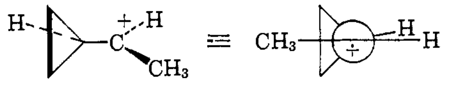
Alternatively, if the ion had a "bisected" geometry[3] (**6** or **7**), inactive products would be expected since **6**



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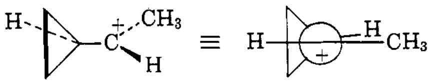

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(1) Alfred P. Sloan Foundation Research Fellow.

(2) Reviewed by H. G. Richey, Jr., in a chapter prepared for "Carbonium Ions," G. A. Olah and P. von R. Schleyer, Ed., to be published by John Wiley and Sons, Inc., New York, N. Y.

(3) N. C. Deno in "Progress in Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., 1964.

(4) Though the following discussion assumes that the cyclopropyl groups of cyclopropyl carbonium ions are not greatly distorted, the problem of distinguishing between crown and bisected geometries would exist even if cyclopropyl rings were greatly altered.

(5) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 3542 (1951); C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145 (1952). This structure has already been eliminated as a possible description since C-1, C-3, and C-4 are not always equilibrated completely in reactions thought to proceed through unsubstituted cyclopropyl carbonium ions (see ref 6).

(6) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(7) M. E. H. Howden and J. D. Roberts, *Tetrahedron*, **19** [2], 403 (1963). Ion **5** is assumed to be in rapid equilibrium with closely related isomers in which C-1, C-3, and C-4 have interchanged positions.