Mercury in Organic Chemistry. III.[1] The Anti-Markovnikov Esterification of Terminal Alkenes

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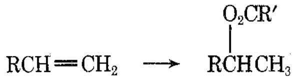
The direct anti-Markovnikov esterification of monosubstituted alkenes can be achieved in excellent yields under very mild reaction conditions using a hydroboration–mercuration–iodination sequence. Hydroboration with "borane" and subsequent mercuration with a variety of mercuric carboxylates gives excellent yields of the corresponding primary alkylmercuric carboxylates. *In situ* iodination generates alkyl iodides which under the reaction conditions are rapidly transformed into primary esters. This procedure does not permit the synthesis of esters derived from very strong carboxylic acids or more highly substituted alkenes.

Although the addition of carboxylic acids to alkenes proceeds readily in accordance with Markovnikov's rule (eq 1),[2] there presently appear to be no convenient, direct synthetic methods available for the anti-Markovnikov esterification of alkenes (eq 2). We wish to report that monosubstituted olefins can be directly converted under very mild reaction conditions to the corresponding primary esters in excellent yield by a sequence involving hydroboration–mercuration–iodination.



$$RCH{=}CH_2 \longrightarrow R\overset{\overset{O_2CR'}{|}}{C}HCH_3 \qquad (1)$$

$$RCH{=}CH_2 \longrightarrow RCH_2CH_2O_2CR' \qquad (2)$$

Results and Discussion

We recently reported a convenient method for the conversion of terminal alkenes into primary alkylmercuric salts *via* hydroboration–mercuration (eq 3, 4).[3] At the same time, Tufariello and Hovey reported that *in situ* bromination of these organomercurials provides a convenient method for the anti-Markovnikov hydrobromination of alkenes (eq 5).[4] We have observed, however, that the *in situ* iodination of these same organomercurials does *not* afford the corresponding alkyl iodides, but provides excellent yields of the primary alkyl acetates instead! In view of this surprising result we have examined the reaction more closely and wish now to report the details of that study.

$$3RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2)_3B \qquad (3)$$

$$(RCH_2CH_2)_3B + 3Hg(OAc)_2 \longrightarrow 3RCH_2CH_2HgOAc + B(OAc)_3 \qquad (4)$$

$$RCH{=}CH_2 \xrightarrow{1/3BH_3} \xrightarrow{Hg(OAc)_2} \xrightarrow{Br_2} RCH_2CH_2Br \qquad (5)$$

The reaction conditions necessary for the conversion of monosubstituted olefins into esters are extremely mild. Both the hydroboration reaction and the subsequent mercuration of the resultant primary trialkylboranes are very facile reactions requiring only minutes at room temperature.[3] The addition of iodine directly to the reaction mixture results in the rapid decolorization of the iodine and the formation of the corresponding primary esters in excellent yield. For example, treatment of a tetrahydrofuran (THF) solution of tri-*n*-butylborane[5] with 3 equiv of mercuric acetate and iodine results in an 81% yield of *n*-butyl acetate and 3% of *n*-butyl iodide. The alkyl iodide completely disappears if a 5–10% excess of mercuric acetate is used. Substitution of diglyme for THF results in a more rapid decolorization of iodine and a 93% yield of pure *n*-butyl acetate. The use of diglyme seems to lead to uniformly higher yields. Using diglyme as described above, we have been able to convert a number of different monosubstituted alkenes into esters in excellent yields. Furthermore, the reaction is not limited to the synthesis of acetates alone. Indeed, mercuric *n*-butyrate and mercuric benzoate also give excellent yields of the corresponding esters. Some representative conversions are summarized in Table I.

Several limitations to this reaction have been observed. Although mercuric acetate, mercuric *n*-butyrate, and mercuric benzoate give excellent yields of esters, mercuric trifluoroacetate gives only very poor yields. Thus, esters of very strong acids may not be accommodated by this reaction sequence. Furthermore, although all monosubstituted alkenes, including 3,3-dimethyl-1-butene, give excellent yields under our reaction conditions, disubstituted terminal alkenes such as isobutylene give only very poor yields and are generally contaminated with large amounts of the corresponding iodide. Finally, trialkylboranes derived from internal olefins do not readily react with mercuric carboxylates.[6] Thus, this procedure appears limited to the synthesis of esters derived from weaker carboxylic acids and monosubstituted olefins.

In view of the tremendous difference in the products of bromination and iodination of the same organomercurials under essentially identical reaction conditions, we have taken a closer look at both of these reactions. It is well known that the halogenation of organomercurials gives the corresponding alkyl halides.[7] This we have confirmed in the case of *n*-butylmercuric acetate. However, *in situ* bromination of the *n*-butylmercuric acetate obtained under our reaction conditions leads to *n*-butyl bromide contaminated with about 10% of *n*-butyl acetate. This result, plus the fact that minor amounts of iodide were evident in our reactions when only stoichiometric amounts of mercuric acetate were used, strongly suggested to us that we must first be forming the alkyl iodide, which was rapidly transformed into the ester. In fact, immediate glpc analysis of the reaction mixture obtained from treatment of tri-*n*-butylborane with mercuric acetate and iodine indicated significant amounts of *n*-butyl iodide which rapidly disappeared.

It is obvious that the other product of the mercuration reaction, namely the boron tricarboxylate, is playing a major role in this reaction. This was confirmed by the following experiments. After the mercuration of tri-*n*-butylborane, addition of methanol (24 hr) and subsequent iodination gave only a 7% yield of *n*-butyl acetate and a 63% yield of *n*-butyl iodide. The methanol presumably removes the boron triacetate (eq 6). Furthermore, the hydroboration–mercuration–iodination of 1-decene using dicyclohexylborane gives only about a 20% yield of *n*-decyl

$$B(O_2CCH_3)_3 + 3HOCH_3 \longrightarrow B(OCH_3)_3 + 3HO_2CCH_3 \qquad (6)$$

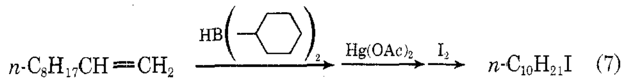
Table I
The Anti-Markovnikov Esterification of Alkenes

$$RCH{=}CH_2 \xrightarrow{{}^1/_3BH_3} \xrightarrow{Hg(O_2R')_2} \xrightarrow{I_2} RCH_2CH_2O_2CR'$$

Registry no.	Alkene[a]	Registry no.	Mercuric carboxylate	Ester	Yield,[b] %
74-85-1	Ethylene	1600-27-7	Mercuric acetate	Ethyl acetate	92
		13257-51-7	Mercuric trifluoroacetate	Ethyl trifluoroacetate	17
		19348-32-4	Mercuric butyrate	Ethyl butyrate	97 (88)
		583-15-3	Mercuric benzoate	Ethyl benzoate	86
106-98-9	1-Butene		Mercuric acetate	*n*-Butyl acetate	93 (84)
			Mercuric butyrate	*n*-Butyl butyrate	84
115-11-7	Isobutylene		Mercuric acetate	Isobutyl acetate	30[c]
563-45-1	3-Methyl-1-butene		Mercuric acetate	Isoamyl acetate	88
558-37-2	3,3-Dimethyl-1-butene		Mercuric acetate	3,3-Dimethyl-1-butyl acetate	73
872-05-9	1-Decene		Mercuric acetate	*n*-Decyl acetate	89

[a] Reference 5. [b] Glpc yield (isolated yield). [c] Contains approximately 20% isobutyl iodide.

acetate and 70–80% of *n*-decyl iodide (eq 7). Thus, dicyclohexylboron acetate is evidently also ineffective in converting the organomercurial into the ester upon iodination.


(7)

The following mechanism seems most consistent with these observations (eq 8–12).

$$3RCH{=}CH_2 + BH_3 \longrightarrow (RCH_2CH_2)_3B \quad (8)$$

$$(RCH_2CH_2)_3B + 3Hg(O_2CR')_2 \longrightarrow RCH_2CH_2HgO_2CR' + B(O_2CR')_3 \quad (9)$$

$$RCH_2CH_2HgO_2CR' + I_2 \longrightarrow RCH_2CH_2I + IHgO_2CR' \quad (10)$$

$$IHgO_2CR' + B(O_2CR')_3 \longrightarrow IHgB(O_2CR')_4 \quad (11)$$

$$IHgB(O_2CR')_4 + RCH_2CH_2I \longrightarrow RCH_2CH_2O_2CR' + HgI_2 + B(O_2CR')_3 \quad (12)$$

Equations 8–10 are all well-known reactions. The presence of the boron tricarboxylate presumably formed in the mercuration step (eq 9) has been shown to be vital to the overall conversion of organomercurial to ester. We suggest that this compound reacts with the iodomercuric carboxylate present from the iodination step (eq 10) to form a species, iodomercuric boron tetracarboxylate (eq 11), capable of displacing the iodide of the alkyl iodide by a carboxylate group (eq 12). The boron tricarboxylate actually serves as a catalyst in this reaction, since it is regenerated in the displacement step (eq 12).

The following observations lend support to this mechanism. The addition of lithium iodide to the organomercurial prior to iodination results in high yields of alkyl iodide, not acetate.[8] Presumably the alkylmercuric iodide is formed. Upon iodination one then obtains mercuric iodide incapable of abstracting another iodide from the alkyl iodide (eq 13, 14). Furthermore, treatment of tri-*n*-butylborane with only 1 equiv of mercuric acetate results in the rapid formation of di-*n*-butylmercury.[9] Iodination of this reaction mixture gives a 98% yield of *n*-butyl iodide and no *n*-butyl acetate (eq 15). At no time is any mercuric acetate derivative present upon iodination. Only mercuric iodide can be formed by the iodination of di-*n*-butylmercury.

$$RCH_2CH_2HgO_2CR' + LiI \longrightarrow RCH_2CH_2HgI + LiO_2CR' \quad (13)$$

$$RCH_2CH_2HgI + I_2 \longrightarrow RCH_2CH_2I + HgI_2 \quad (14)$$

$$(n\text{-}C_4H_9)_3B + Hg(OAc)_2 + 2I_2 \longrightarrow 2n\text{-}C_4H_9I + HgI_2 + n\text{-}C_4H_9B(OAc)_2 \quad (15)$$

We have also attempted to reproduce the reactions outlined in eq 11 and 12. Mercuric acetate is relatively insoluble in THF. Addition of 1 equiv of mercuric iodide results in a clear solution, suggesting the formation of iodomercuric acetate. Treatment with *n*-butyl iodide for 24 hr at room temperature gave only a 9% yield of *n*-butyl acetate, but addition of 10% of boron triacetate (prepared from "borane" and acetic acid) gave a 55% yield of ester. Similarly, mercuric acetate does not react in 24 hr with *n*-butyl iodide at room temperature, but gives an 88% yield of *n*-butyl acetate in a little over 1 hr in the presence of 10% boron triacetate (eq 16).[10] On the other hand, isobutyl iodide gives only a very poor yield of isobutyl acetate under these same conditions, thus explaining our earlier poor results with isobutylene. Mercuric trifluoroacetate also yields very little of the corresponding ester. *n*-Butyl bromide fails to react at all under identical conditions. This result explains the vast difference in products in the bromination and iodination reaction sequences. We are currently exploring the scope of these alkyl halide esterification reactions and will report on this work shortly.

$$CH_3CH_2CH_2CH_2I + Hg(OAc)_2 \xrightarrow{B(OAc)_3} CH_3CH_2CH_2CH_2OAc + IHgOAc \quad (16)$$

Thus, the many unusual observations made during the course of this investigation on the hydroboration–mercuration–iodination of alkenes are all consistent with the mechanism outlined above. In view of the many reactions actually involved in this reaction sequence, it is indeed amazing that such excellent yields of esters can be obtained. Each step from alkene to organoborane, organomercurial, alkyl iodide, and finally ester must be proceeding in near quantitative yield.

Experimental Section

Materials. Most materials, solvents, and chemicals used have been described previously.[3] Triethylborane and tri-*n*-butylborane were used directly as obtained from Callery Chemical Co. The preparations of mercuric *n*-butyrate, benzoate, and trifluoroacetate have been described previously.[6] Mercuric benzoate is best dried over phosphorus pentoxide under a high vacuum for several days.

Hydroboration–Mercuration–Iodination of Representative Alkenes. Although the hydroboration–mercuration of all alkenes using both "borane" and dicyclohexylborane has been described previously,[3] the following synthesis of *n*-butyl acetate is illustrative. A dry 300-ml flask equipped with septum inlet, pressure-equalizing addition funnel, and magnetic stirrer was flushed with nitrogen and maintained under a static pressure of gas. To 100 ml of 0.33 *M* tri-*n*-butylborane (8.13 ml = 33.3 mmol) in diglyme was added at 0° 35.06 g (110 mmol) of mercuric acetate while backflushing with nitrogen. After stirring for 10 min at 0°, 55 ml (110 mmol) of a solution of 2 *M* iodine in diglyme was slowly added. The resulting solution was stirred overnight at room temperature.

Addition of ether, decolorization of excess iodine with aqueous sodium thiosulfate, washing with 5 × 100 ml of 5 *M* potassium iodide or 3 *M* sodium thiosulfate (to remove mercuric iodide) and 2 × 100 ml of saturated sodium bicarbonate, decolorization with activated carbon, and drying over anhydrous sodium sulfate gave a solution which upon distillation yielded 9.82 g (84%) of *n*-butyl acetate.

All yields determined by glpc analysis were run in a similar fashion on a 10-mmol scale using a suitable hydrocarbon internal standard. The exact experimental procedures used for hydroboration-mercuration are those reported earlier.[3] THF is readily removed under vacuum and replaced by dry diglyme. In those reactions in which diglyme interferes with the distillation of the desired ester, THF is recommended as a reaction solvent, although slightly lower yields are generally obtained.

All organoboranes prepared from monosubstituted alkenes by hydroboration in THF possess 6% of *sec*-alkylboron groups which will not react.[3] Thus 10% less mercuric acetate and iodine were used and all yields were based on available primary alkylboron groups.

The Boron Triacetate Catalyzed Conversion of *n*-Butyl Iodide to Acetate. Ten milliliters of 0.1 *M* boron triacetate was prepared by addition of 0.42 ml (1 mmol) of 2.4 *M* "borane" in THF to 9.4 ml of THF containing 0.18 g (3.0 mmol) of acetic acid at −78°. After removal of the cold bath, this solution was stirred for 3 hr at room temperature. To this solution was added 1.84 g (10 mmol) of *n*-butyl iodide, the appropriate amount of mercuric acetate (5 or 10 mmol) and/or mercuric iodide (5 mmol), and 0.8 ml of nonane as an internal standard. Glpc analysis indicated the extent of reaction.

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References and Notes

(1) Part II: R. C. Larock, *J. Organometal. Chem.*, in press.
(2) J. Guenzet and M. Camps, *Tetrahedron Lett.*, 2647 (1972), and references cited therein.
(3) R. C. Larock and H. C. Brown, *J. Amer. Chem. Soc.*, **92**, 2467 (1970).
(4) J. J. Tufariello and M. M. Hovey, *J. Chem. Soc. D*, 372 (1970); *J. Amer. Chem. Soc.*, **92**, 3221 (1970).
(5) Pure triethylborane and tri-*n*-butylborane were used directly as obtained commercially. All other organoboranes were prepared *via* hydroboration of the appropriate alkene and thus sometimes contain minor amounts (up to 6%) of secondary alkyl groups which will not react.
(6) R. C. Larock and H. C. Brown, *J. Organometal. Chem.*, **26**, 35 (1971).
(7) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968.
(8) J. J. Tufariello, private communication.
(9) J. D. Buhler and H. C. Brown, *J. Organometal. Chem.*, **40**, 265 (1972).
(10) Further details on this interesting reaction will be reported shortly.

Polarographic and Spectrophohotometric Evaluation of Acid Dissociation Constants of Some Substituted Ethyl Benzoylacetates

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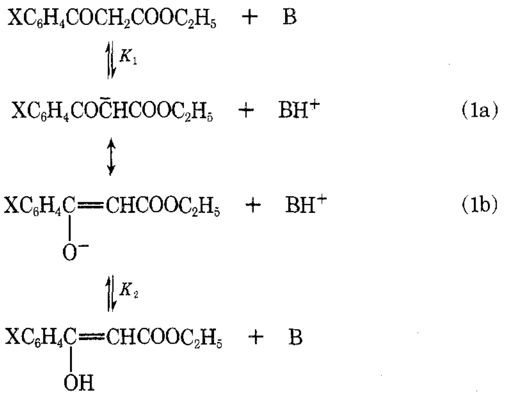
The overall dissociation constants K_Σ of ethyl benzoylacetate and *p*-methoxy, -methyl, -chloro, and -cyano derivatives were evaluated spectrophotometrically and polarographically, and [enol]/[keto] ratios were measured by titration with bromine. Values of the dissociation constants of the keto (K_1) and enol (K_2) forms were isolated; like polarographic half-wave potentials, they were shown to be linear functions of Hammett substituent constants $\sigma_{p\text{-X}}$.

In alkaline solutions of β-keto esters, the keto and enol forms dissociate to give a common conjugate base, the carbanion enolate (eq 1). When spectrophotometry is used for the study of such an equilibrium, the only condition which must be fulfilled is that the equilibrium must be established before the spectrum is recorded. However, with methods such as bromination, which involve a chemical interaction of either the keto form or the enol, it is essential that the establishment of the keto-enol equilibrium be slow in comparison with the competing reaction. Information on the rate of establishment of this equilibrium, which is of interest with respect to the general reactivity of the carbonyl compound, can be obtained by polarography. Using accepted criteria,[1] it is possible to show whether the limiting current is governed by diffusion or by the rate of chemical reaction. If, for a system at equilibrium, the limiting current of one species is diffusion controlled, the rate of establishment of the equilibrium must be much lower than the rate of the mass transport by diffusion. This has been found to be true for unsubstituted ethyl benzoylacetate.[2]



$$
\begin{array}{lr}
\mathrm{XC_6H_4COCH_2COOC_2H_5} + \mathrm{B} & \\
\big\downarrow\!\uparrow K_1 & \\
\mathrm{XC_6H_4CO\bar{C}HCOOC_2H_5} + \mathrm{BH^+} & \text{(1a)}\\
\updownarrow & \\
\mathrm{XC_6H_4\underset{O^-}{\underset{|}{C}}{=}CHCOOC_2H_5} + \mathrm{BH^+} & \text{(1b)}\\
\big\downarrow\!\uparrow K_2 & \\
\mathrm{XC_6H_4\underset{OH}{\underset{|}{C}}{=}CHCOOC_2H_5} + \mathrm{B} &
\end{array}
$$

It was of interest to investigate phenyl-substituted benzoylacetates to follow the substituent effects on the acid-base and keto-enol equilibria and to show whether the presence of substituents affects the relatively slow rate of establishment of equilibrium 1.

In view of the nature of system 1, it seemed preferable to attempt first separation of the two acid dissociation constants K_1 and K_2 from experimental data rather than to try to express the substituent effects on the [enol]/[keto] ratio.

Values of K_1 and K_2 are usually not directly accessible to measurement, but they can be calculated from two kinds of measurable quantities: The first of these is the value of the overall acid-base dissociation constant K_Σ, defined by the expression K_Σ = [carbanion enolate][H^+]/([keto form] + [enol form]). The value of K_Σ is re-