STUDY OF THE ENOL BORINATE
CLAISEN REARRANGEMENT

by

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

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STUDY OF THE ENOL BORINATE CLAISEN REARRANGEMENT
INTRODUCTION

Rearrangement reactions are of valuable synthetic utility to the organic chemist. In particular, the Claisen rearrangement has been one of the most thoroughly investigated rearrangement reactions. Variations of the Claisen rearrangement have also been studied and are of current interest. This project was undertaken in order to investigate a variation of the Claisen rearrangement which proceeds through an enol borationate intermediate.
HISTORICAL

The Claisen rearrangement\textsuperscript{1} is a [3,3] sigmatropic rearrangement that occurs via a concerted mechanism, thus allowing highly predictable stereospecificity.

Examples of Claisen rearrangements are known in which various combinations of carbon, oxygen, nitrogen, and sulfur occupy places in the reacting system. However, in most cases carbon atoms are involved in five of the centers and $X$ is oxygen. In these cases a vinyl allyl ether is generated by any of the conventional methods. Heating the ether causes a thermal rearrangement and formation of a $\gamma,\delta$-unsaturated carbonyl compound.

These rearrangements generally take place at high temperatures which is somewhat of a disadvantage, especially when working with molecules which are thermally unstable or contain thermally unstable substituents.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {$\xrightarrow{195^\circ}$};
\end{tikzpicture}
\end{center}
Ireland\textsuperscript{3} has investigated a variation of the Claisen rearrangement. He has found that the esters of allyl alcohols can be rearranged to \( \gamma, \delta \)-unsaturated carboxylic acids \textit{via} the trimethylsilyl derivative of the ester enolate. The ester enolate is generated and trapped with trimethylsilyl chloride. It is then found to rearrange quite rapidly at room temperature.

The enolate Claisen rearrangement has been shown to be a useful procedure for obtaining carboxylic acids and is also useful for the synthesis of natural products due to the stereospecificity of the reaction. With this in mind, it was thought that other methods of generating the enolate of esters might also be useful for obtaining the rearrangement.
One method of obtaining the enolate is through the use of trialkylboranes as alkylating agents. The use of these organoboranes as such has been developed quite extensively as of late. Trialkylboranes undergo a facile 1,4-addition to \( \alpha, \beta \)-unsaturated aldehydes and ketones. They also react with \( \alpha \)-diazocarbonyl compounds resulting in the transfer of an alkyl group and the displacement of nitrogen.\(^4\)

In 1967, Brown\(^5\) postulated the existence of enol borinates, i.e., an enolate in which the carbonyl oxygen is complexed with the organoborane, in the 1,4-addition of a trialkylborane to methyl vinyl ketone. In 1968, Hooz\(^6\) also recognized the possibility of an enol borinate in the reaction of trialkylboranes with ethyl diazoacetate.

\[
\begin{align*}
R_3B + \begin{array}{c}
\text{1} \\
\end{array} & \rightarrow \begin{array}{c}
\text{R} \\
\end{array} \begin{array}{c}
\text{O-} \\
\end{array} \begin{array}{c}
\text{BR}_2 \\
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
R_3B + \begin{array}{c}
\text{2} \\
\end{array} & \rightarrow \begin{array}{c}
\text{R} \\
\end{array} \begin{array}{c}
\text{O-} \\
\end{array} \begin{array}{c}
\text{BR}_2 \\
\end{array} \\
\end{align*}
\]
In 1971, evidence for the existence of the enol borinate was firmly established when Pasto and Wojtkowski isolated and characterized several of these enol borinates. 7

Knowledge of the existence of an enol borinate along with the ester enolate Claisen rearrangement prompted the following study.
RESULTS AND DISCUSSION

The goal of this project was to utilize the enol borinate in order to expect a Claisen rearrangement of the intermediate formed during the $\alpha$-alkylation of the esters of allylic alcohols.

First prepared was trans-crotyl diazoacetate, $^5$, by the combination of glyoxyl chloride hydrazone, $^4$, with trans-crotyl alcohol, $^3$, in the presence of triethylamine. $^9$ The organoborane chosen for reaction with the diazoester was tri-$\eta$-hexyl borane, $^6$, which was prepared, in situ, by the reaction of $\alpha$-hexene with commercial borane in tetrahydrofuran. $^8$

Crotyl diazoacetate and tri-$\eta$-hexyl borane were combined with the idea that the reaction would proceed through the enol borinate intermediate, $^7$. However, the time and temperature required for a rearrangement to occur were not known. Following a literature preparation for the reaction of tri-$\eta$-hexyl borane with a different diazoester, $^6$ the mixture was stirred for 0.5 h. at 0° and then for an additional 2 h. at room temperature. The mixture was worked up to yield crotyl octanoate, $^8$, in 44%. Due to an $\text{-OH}$ stretch in the IR spectrum, it was assumed that the crude product also contained some of the hydrolyzed borane carrying the two unreacted alkyl groups. This impurity was removed, but not isolated, by filtering the mixture through a silica gel column and eluting with 5% ether/hexane. In
subsequent trials, in an effort to improve the yield of the ester, the residual organoboranes in the mixture were oxidized with hydrogen peroxide and sodium acetate prior to workup. 8

The above procedure was again followed with the addition of the organoborane oxidation step. the yield of crotyl octanoate was 55\% by glpc analysis. Glpc analysis of the crude reaction mixture showed that there was also 1-hexanol present to the extent of 15\%. Further evidence for the presence of the ester and alcohol was obtained by finding that the retention times on the glpc were the same as those of authentic samples of both of these compounds. It is believed that the alcohol is being formed by the anti-Markovnikov addition of borane to hexene followed by oxidation with base and hydrogen peroxide.

At this point, no rearrangement product had been obtained in any of the attempts. In an effort to effect rearrangement, the reaction time was increased to 5 h. before it was quenched with water. Also, up until this time, the reaction had been carried out under a stream of nitrogen. It was thought that the presence of air in the nitrogen line could become quantitive and destroy the enol borinate intermediate. To reduce the threat of large amounts of oxygen entering the reaction vessel with the nitrogen, the reaction setup was changed in order to provide for a static pressure of nitrogen

*The ester was also prepared by the reaction of octanoyl chloride with trans-crotyl alcohol in the presence of excess pyridine.
in the apparatus.

The reaction was carried out with the described changes to yield 3% of acid, 10, 40% of ester, 8, and slightly less than 10% of 1-hexanol (by NMR integration).

Other attempts of the reaction with extended stirring times did not yield the acid in any detectable amounts. With the acid once obtained, it was of interest to improve the yield. A look at the intermediate in the reaction shows that there may be a competition between two intermediates, 7 and 11.

\[
\begin{align*}
&\text{O-B(\(\text{n-C}_6\text{H}_{13}\))}_2 \\
&\text{(\(\alpha-C_6\text{H}_{13}\))}
\end{align*}
\quad \leftrightarrow \quad
\begin{align*}
&\text{O-B(\(\text{n-C}_6\text{H}_{13}\))}_2 \\
&\text{(\(\text{n-C}_6\text{H}_{13}\))}
\end{align*}
\]

It was thought that heating the reaction mixture prior to hydrolysis of the intermediate might drive this equilibrium toward the enol borinate tautomer, 7. Also, in noting the thermodynamic requirements of the Claisen rearrangement in a classical sense, it was thought that heating would facilitate electron migration, thus forcing rearrangement. After addition of crotyl diacetate to the tri-\(\text{n}\)-hexyl borane, the mixture was heated at 67\(^\circ\) for 2 h. Workup of the mixture afforded acid, 10, in a 2.8% yield. Extending the heating period to six hours did not have an effect on the rearrangement as the acid
was isolated in a 2.5% yield. The yield of ester, \( \text{E} \), in each of the attempts was 51% and 47% respectively. Also, 1- hexanol was present in amounts not exceeding 10%. The following table summarizes the results of the experiments:

<table>
<thead>
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<th>Reaction Temp.</th>
<th>Time</th>
<th>Yield</th>
<th>Yield</th>
</tr>
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<tr>
<td>( 22^\circ )</td>
<td>2 h.</td>
<td>44 %</td>
<td>-</td>
</tr>
<tr>
<td>( 22^\circ )</td>
<td>2 h.</td>
<td>55 % *</td>
<td>-</td>
</tr>
<tr>
<td>( 22^\circ )</td>
<td>5 h.</td>
<td>40 %</td>
<td>3 %</td>
</tr>
<tr>
<td>( 67^\circ )</td>
<td>2 h.</td>
<td>51 %</td>
<td>2.8 %</td>
</tr>
<tr>
<td>( 67^\circ )</td>
<td>6 h.</td>
<td>47 %</td>
<td>2.5 %</td>
</tr>
</tbody>
</table>

* The residual organoboranes were oxidized with hydrogen peroxide and sodium acetate in this attempt.

The Claisen rearrangement has been shown to proceed through a chair-like transition state in the absence of any unusual steric constraints.\(^{12}\) The same has been illustrated for the enolate Claisen rearrangement.\(^{3}\) The transition state can proceed through either of two conformations, \( A \) or \( B \).
Due to the equatorial disposition of R in B, there is minimal steric interaction between R and X. Hence this conformation will be lower in energy and the preferred one in the transition state. The result of conformation B is the formation of a trans double bond.

![Diagram of conformation B with a trans double bond]

It can be postulated that the enol borinate Claisen rearrangement proceeds through a similar chair-like transition state, taking upon the conformation that most effectively relieves any steric interactions. In this case, R' is n-hexyl and R is hydrogen.

![Diagram of conformation B' with R' and R exchanged]

Steric interactions between the bulky -OB\(_2\)R\(_2\) group and R are virtually non-existent in conformation B'. Any rearrangement which occurred via an enol borinate intermediate, presumably proceeded through such a transition state.

The conformational requirements for a Claisen rearrangement seem to be obeyed by the enol borinate intermediate. However, low yields were obtained in each case where rearrange-
ment had occurred.

A factor not yet explored is the possibility of rearrangement occurring at temperatures higher than those tried. Enolate Claisen rearrangements have been known to require temperatures approaching $67^\circ$. The enol borinate intermediate may require temperatures above $67^\circ$ in order to effect a rearrangement. However, this possibility has not been investigated.
EXPERIMENTAL

Proton magnetic resonance spectra were recorded on the Varian EM 390 spectrometer and the T-60 spectrometer. All proton magnetic resonance spectra were determined in carbon tetrachloride solution using tetramethyldisilane as an internal standard. All infrared spectra were determined on a Perkin-Elmer 137 infrared spectrophotometer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Gas chromatography was performed on the Varian Aerograph Model 90-P instrument using a 20% SE-30 on Chrom-sorb W(60/80 mesh) column of size 7.5 ft by 1/4 in.

Elemental analyses were performed in the University of Illinois microanalytical laboratory. The tetrahydrofuran used was dried with calcium hydride and distilled from sodium and benzophenone.
Glyoxyl chloride hydrazone (4). Commercial glyoxylic acid (74.04 g, 0.50 mol) and p-toluene sulfonyl hydrazone (96.00 g, 0.50 mol) were combined to form glyoxylic acid hydrazone (78.60 g, 45%): mp 151-154° (Lit. mp 148-154°). Treatment of the acid hydrazone (50.20 g, 0.21 mol) with thionyl chloride (49 g, 0.42 mol) gave 4 (24.2 g, 45%): mp 104-112° (Lit. mp 101-112°).

trans-Crotyl diazoacetate (5). Triethylamine (7.80 g, 0.077 mol) in 25 mL of dichloromethane is added to a cooled (0°) solution of 10.0 g (0.038 mol) of glyoxyl chloride hydrazone and 2.80 g (0.038 mol) of crotyl alcohol in 100 mL of dichloromethane. The solution is stirred at 0° for 1 h. and the solvent is removed at 25° under reduced pressure. The residual dark orange liquid in 200 mL of benzene is thoroughly mixed with 100 g of Florisil, filtered and washed with 3 portions of benzene. The solvent is removed at 25° to give a yellow liquid which upon distillation under reduced pressure affords 2.40 g (45%) of diazoester 5: bp. 48-51° (0.30 mm), (Lit. bp. 30-33° at 0.15 mm). IR(film) 2100, 1690 cm⁻¹.

General procedure for the reaction of tri-\(\text{-n}\)-hexyl borane with crotyl diazoacetate. Commercial borane in tetrahydrofuran (10.8 mL of a 1.02 M solution, 11 mmol) is added to a cooled (0°) solution of 2.78 g (33 mmol) of 1-hexene in 15 mL of tetrahydrofuran. The mixture is stirred for one hour under a static pressure of nitrogen. The tri-\(\text{-n}\)-hexyl borane is ready for use in the next step.
To the solution of tri-n-hexyl borane is added 1.40 g (10 mmol) of crotyl diazoacetate in 12 mL of tetrahydrofuran while the temperature is maintained at 0°C. The solution is then stirred and/or heated for the time and temperature specified in the table. Water (2 mL, 111 mmol) is then added to the mixture while the temperature is kept at 0°C. The mixture is then heated at reflux for 1 h. A solution of 7.3 mL of 3 N sodium acetate is added followed by the dropwise addition of 2.3 mL of 30% hydrogen peroxide while maintaining the reaction temperature below 20°C. The mixture is then allowed to stir at room temperature for 1 h.

The organic phase is separated, concentrated on a rotary evaporator, poured into water, and extracted into an ether phase. The ether phase is extracted with 3 30-mL portions of 5% sodium bicarbonate. The bicarbonate extracts are combined, acidified to pH 1, and extracted into a separate ether phase. The ether is dried over anhydrous magnesium sulfate and the solvent removed. Acid 10 (if it formed) is collected as a clear liquid in the yield indicated in the table. The initial ether extracts are treated in a similar manner to yield crotyl octanoate as a clear liquid and 1-hexanol. The crotyl octanoate was separated and purified by preparative gas chromatography. trans-crotyl octanoate: IR(film) 1740 cm⁻¹ (C=O); ¹H NMR δ = 5.55 (m, 2H, CH=CH), 4.54 (d, slight contamination of cis-isomer, CH₂-O, J=6), 4.37 (d, 2H, CH₂-O, J=6), 2.28 (t, 2H,
CH₂-C=O, J=6), 1.70(d, 3H, vinyl CH₃, J=6), 1.28(br s, 10H), 0.88 (t, 3H, J=6).


2-n-Hexyl-3-methyl-4-pentoic acid. IR(film) 3100-2600(broad), (-OH), 1700 cm⁻¹ (C=O); ¹H NMR = 10.80(s, 1H, COOH), 5.50(m, 1H, CH=CH₂), 4.95(m, 1H, CH=CH₂, cis-H only), 4.80(br s, 1H, CH=CH₂, trans-H only), 2.24(m, 2H, R₂CH-CHR-C=O), 1.21(br s, 10H), 0.98(d, 3H, -methyl, J=6), 0.80(br t, 3H, J=6).

Crotyl octanoate. A solution of 5.0 g (0.035 mol) of octanoic acid and 2.5 g (0.018 mol) of phosphorous trichloride were heated at 55°C for 1 h. The acid chloride is decanted from the residual phosphonic acid and distilled to give 3.3 g (58%) of octanoyl chloride: bp. 198-203°C (Lit.¹¹ bp. 196°C).

A solution of 1.0 g (0.0062 mol) of octanoyl chloride and 0.45 g (0.0062 mol) of crotyl alcohol was refluxed in benzene. A solution of 0.49 g (0.0062 mol) of pyridine in 10 mL of benzene was added dropwise with stirring. The mixture is then allowed to stir at room temperature for 1 h. The solvent was evaporated and the remaining product dissolved in ether and extracted with 5% hydrochloric acid in order to remove any residual pyridine. The ether phase was dried over anhydrous magnesium sulfate and the solvent evaporated to give 0.53 g (43%) of crotyl octanoate as a clear liquid. IR(film) 1740 cm⁻¹ (C=O); ¹H NMR = 5.54(m, 2H, CH=CH), 4.38(d, 2H, O-CH₂, J=6),
2.28 (m, 4H, CH$_2$-CH$_2$-C=O), 1.70 (d, 3H, vinyl CH$_3$, J=6), 1.30 (br s, 10H), 0.88 (t, 3H, J=6).

Obtaining a rearrangement product in some of the experiments performed verifies the existence of the enol borinate intermediate. However, the optimum conditions for rearrangement have not been worked out at the present time. This reaction could be very useful in the area of synthetic chemistry should future researchers develop it further. The enol borinate Claisen rearrangement provides simultaneous alkylation and rearrangement while eliminating the base catalyzed enolate generation step.
REFERENCES


