A favorable method for the synthesis of benzyl methyl ketone and its derivatives is elucidated. The oxidation of α-methylstyrenes with iodosylbenzene diacetate was studied. For the preparation of benzyl methyl ketone, iodosylbenzene diacetate was found to be an oxidant superior to lead tetraacetate. Under optimum reaction conditions, the yield and selectivity of benzyl methyl ketone were 93% and 93%, respectively. The reactions proceeded effectively in acetic acid-water mixture, in the presence of sulfuric acid. The studies on using a competitive reaction method revealed that reactivities of the substituted α-methylstyrene derivatives satisfied the Hammett equation with a negative $\rho$ value of $-2.56$. A logical reaction mechanism involving shift of phenyl group is proposed.

1. Introduction

Benzyl methyl ketone is an intermediate material useful for the preparation of medicines such as an antihypertensive agent, L-α-methyldopa. Norman and co-worker have reported on the preparation of benzyl methyl ketone by treating α-methylstyrene with lead tetraacetate. Generally, the unsaturated hydrocarbons react with lead tetraacetate to give high yields of 1,2-diacetoxy compounds. The reaction of α-methylstyrene with this system, however, did not lead to 1,2-diacetoxy-1-phenylethane, but led to benzyl methyl ketone.

On the other hand, iodosylbenzene diacetate have been used to promote the cracking of glycols, the oxidation of unsaturated compounds, and the diazotization of primary amines. A study on the oxidation of unsaturated hydrocarbons with iodosylbenzene diacetate and lead tetraacetate, revealed that the distribution of reaction products with the former oxidant in accord with that using the latter. Shimizu and co-workers have recently discovered that the main product formed by treating α-methylstyrene with iodosylbenzene diacetate was identical to that formed with lead tetraacetate, and that with iodosylbenzene diacetate, the yield of the product increased. No mention has been made of the role of the oxidant, however. We are, thus, interested in the reaction mechanism of formation of benzyl methyl ketone, in this reaction system. This paper elucidates the studies on the formation of benzyl methyl ketone by the reaction of α-methylstyrene with iodosylbenzene diacetate and the application thereof to the oxidation of a series of α-methylstyrene derivatives.

2. Experimental

2.1 Materials

Commercial α-methylstyrene, p-fluoro-α-methylstyrene, and p-chloro-α-methylstyrene were washed with aqueous 10% sodium carbonate and water, dried over calcium chloride, and distilled under reduced pressure. Acetic acid and other organic solvents were dried by usual methods and distilled under argon. Iodosylbenzene diacetate was prepared by treating iodobenzene with 40% peroxyacetic acid-acetic acid mixture, according to the method appearing in the literature; m.p. 158—160°C. Standard benzyl methyl ketone was prepared by hydrolysis and decarboxylation of α-phenylacetoacetonitrile according to a published method, and purified via benzyl methyl ketone sodium bisulfite to a purity of 99.7% (checked by gas chromatography). Other chemicals of reagent grade were used without any further purification.

2.2 Synthesis of p-Methyl-α-methylstyrene

A 300-cm$^3$ round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, a drop-
ping funnel and a thermometer was used, in which were placed 0.15 mol of magnesium ribbon, 0.04 mol of p-bromotoluene and 15 cm³ of ether. The mixture was heated up to the beginning of reaction, and then cooled; to this mixture 75 cm³ of ether and 0.11 mol of p-bromotoluene were added through a dropping funnel. After some time, 0.16 mol of acetone and 10 cm³ of ether were added by droplets to the reaction mixture. The mixture was stirred for a while; and to this, 25% aqueous ammonium chloride was added. The ether-layer was separated from aqueous mixture, ether being removed by evaporation. The residue was refluxed for 1.5 h in 20% aqueous sulfuric acid, and an oily substance was separated from the mixture, and distilled in vacuo; yield 46%, b. p. 65°C/1.2×10⁸ Pa. 1H-NMR (CDCl₃): δ=2.1 (3H, s, CH₃-C), 2.3 (3H, s, CH₃-C₆H₄-), 5.2 (2H, d, CH₂=C), 7.2 (4H, q, –C₆H₄–).

2.3 General Procedure for Reaction of α-Methylstyrenes with Iodosylbenzene Diacetate

A Schulenk-type tube was used, in which were placed 0.5 mmol of iodosylbenzene diacetate and 5 cm³ of aqueous 50% acetic acid. The mixture was stirred for a while; to this mixture 0.5 mmol of α-methylstyrenes was added. The mixture was treated for 2 h at room temperature under argon. The mixture was, then, neutralized by aqueous sodium hydrogencarbonate. An oily substance was extracted with ether. The ether-layer was dried over anhydrous magnesium sulfate, followed by evaporation. The residue was submitted to gas chromatography.

3. Results and Discussion

3.1 Reaction Conditions and Products

Since α-methylstyrene is not readily soluble in aqueous acetic acid, the reaction was carried out in a heterogeneous system. Time-dependencies of conversion of the oxidation of α-methylstyrene with iodosylbenzene diacetate were investigated in a batch operations. The results obtained are shown in Fig. 1. As can be seen from Fig. 1, the reaction was completed within a period of 2 h at room temperature. Analysis by GC-MS of the reaction products showed that there were large amounts of benzyl methyl ketone and iodobenzene, and a very small amount of 2-acetoxy-2-phenyl-1-propanol and others. The selectivities of benzyl methyl ketone were approximately constant, regardless of its reaction time.

The reactions were, then, carried out in systems of different solvents. In benzene, α-methylstyrene was unchangeable. In acetone–water and ethanol–water systems, the results were similar to that in water, while, acetic acid–water system was found to be the best solvent to give good yield of benzyl methyl ketone. These results are summarized in Table 1. The data indicate that water is necessary for the reaction. The effect of concentration of acetic acid on the reaction was studied. The results are shown in Figs. 2, 3, and 4. The reactions at room temperature resulted in high conversion and selectivity over a wide range of concentration of acetic acid. On the other hand, reaction at temperature below 10°C, with the treatment in aqueous 60% acetic acid, resulted in maximum of both conversion and selectivity. The conversion decreased with the decrease in acetic acid content. This is attributed to a decrease in solubility of iodosylbenzene diacetate. The decrease of conversion with high acetic acid content suggests that the role of water molecules in the reaction is significant.

On the other hand, it has been reported that α-methylstyrene was oxidized with lead tetaacetate in acetic anhydride to give benzyl methyl ketone.

![Fig. 1 Time Dependence of Oxidation](image-url)

**Table 1 Effect of Solvent**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion [%]</th>
<th>Benzyl methyl ketone yield [%]</th>
<th>Selectivity [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₆</td>
<td>&lt;1</td>
<td>6.9</td>
<td>27</td>
</tr>
<tr>
<td>Aceton/H₂O (50/50)</td>
<td>25</td>
<td>7.2</td>
<td>28</td>
</tr>
<tr>
<td>EtOH/H₂O (50/50)</td>
<td>25</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>AcO/H₂O (50/50)</td>
<td>&gt;99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Reaction conditions: α-Methylstyrene, 0.5 mmol; Iodosylbenzene diacetate, 0.5 mmol; Solvent, 5.0 ml; Temp., Room temp.; Time, 2 h; under Ar.

b) Obtained by gas chromatography.
with a yield of 46%\(^1\). When this oxidation was carried out in 60% aqueous acetic acid, the conversion of \(\alpha\)-methylstyrene and the selectivity of benzyl methyl ketone were 77 and 78%, respectively, compared with 99 and 81%, respectively, in the oxidation with iodosylbenzene diacetate under the same conditions. It was found, therefore, that iodosylbenzene diacetate has an oxidizing ability superior to that of lead tetraacetate.

The effect of the amount of iodosylbenzene diacetate on the reaction is shown in Fig. 5. It is apparent that 0.5 mmol or more of iodosylbenzene diacetate is necessary for completing the oxidation of \(\alpha\)-methylstyrene. The presence of excess amounts of iodosylbenzene diacetate, however, causes a decrease in the yield of benzyl methyl ketone. Such a decrease in the yield may occur through the acetoxylation of benzyl methyl ketone with iodosylbenzene diacetate\(^7\).

3.2 Reaction of Substituted \(\alpha\)-Methylstyrene Derivatives and Related Compounds

The effect of substituent on the yield of benzyl methyl ketone derivatives was studied. The results are shown in Table 2. It can be seen that an electron-donating group was effective in the high yield of substituted benzyl methyl ketone derivatives. The relative reaction rates of \(\alpha\)-methylstyrene derivatives, therefore, were determined, by using a competitive reaction.

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Table 2: Reaction of Substituted \(\alpha\)-Methylstyrene Derivatives

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Yield</th>
<th>Reaction Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3)</td>
<td>77%</td>
<td>0.5</td>
</tr>
<tr>
<td>(\text{OCH}_3)</td>
<td>81%</td>
<td>0.7</td>
</tr>
<tr>
<td>(\text{Cl})</td>
<td>65%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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The logarithm of relative yields of substituted benzyl methyl ketone derivatives to benzyl methyl ketone was plotted relative to the values of $\sigma$ for three substituents. The result is shown in Fig. 6. Calculation based on the gradient of the straight line gave a negative value of $-2.56$. The negative gradient of the straight line suggests that the reaction of substituted $\alpha$-methylstyrene derivatives are aided by supply of electrons to the benzene ring, whereas those are made more difficult by withdrawal of electrons.

On the other hand, in a way similar to that described for $\alpha$-methylstyrene, the reaction of 1,1-diphenylethylene produced benzyl phenyl ketone, as expected. The expected 2-hexanone, however, was not formed by the reaction with 2-methyl-1-pentene. These results support the logic that the mechanism for structural changes from $\alpha$-methylstyrene to benzyl methyl ketone involves a reaction step in which the phenyl group rearranges, as described above.

### 3.3 Recommended Reaction Mechanism

When $\alpha$-methylstyrene was treated with iodosylbenzene diacetate, it has been reported that the olefins are oxidized with iodosylbenzene to produce the corresponding epoxides. It is assumed, therefore, that $\alpha$-methylstyrene is oxidized to benzyl methyl ketone via an intermediate, $\alpha$-methylstyrene oxide. The oxidation passing through $\alpha$-methylstyrene oxide, however, is negative, because the epoxide was not formed by the reaction of $\alpha$-methylstyrene with iodosylbenzene diacetate. In this manner, the true active species for the oxidation of $\alpha$-methylstyrene with iodosylbenzene seem to be iodosylbenzene diacetate because iodosylbenzene is susceptible to change to iodosylbenzene diacetate in acetic acid.

Table 3 shows the effect of additives on the reaction of $\alpha$-methylstyrene with iodosylbenzene diacetate. As shown in Table 3, the reaction proceeded slightly in water and absolute acetic acid. In acetic anhydride, iodosylbenzene diacetate showed low reactivity as compared with that of lead tetraacetate. While the reactivity increased markedly with addition of a few drops of sulfuric acid the 10% aqueous acetic acid. This result is particularly surprising in view of the fact that the reactivity is not exceptionally great in 10% aqueous acetic acid. The addition of base, such as sodium acetate and potassium hydroxide, did not serve to accelerate the reaction. These results indicate that proton plays an important role in the activation of iodosylbenzene diacetate.

On the basis of various results described above, a reasonable reaction mechanism is proposed as follows:

\[
\text{PhI(OAc)}_2 + H^+ \rightarrow \text{PhI} + \text{OAc} + \text{AcOH} \tag{1}
\]

\[
\text{Ar} \quad \text{CH}_2=\text{C}-\text{CH}_2 + \text{PhI(OAc)}_2 \rightarrow \text{CH}_2=\text{C}-\text{CH}_2\text{Ph} + \text{OAc} \tag{2}
\]
It is known that lead tetraacetate dissociates in acetic acid as follows:

\[
Pb(OAc)_4 \rightarrow Pb^{\text{III}}(OAc)_3 + AcO^- \quad (5)
\]

The lead triacetate ion dissociated should be a reactive electrophile. Since the reactivity of iodosylbenzene diacetate is similar to that of lead tetraacetate, iodosylbenzene monoacetate ion, formed in Eq. (1), probably acts as a strong electrophile. The reactivity of iodosylbenzene diacetate, therefore, is low in water, absolute acetic acid and acetic anhydride, because of a low concentration of such ionic species, and further, the concentration of iodosylbenzene monoacetate ions decreases with the presence of hydroxide ions and acetate ions. This is undesirable for the secondary step, Eq. (2), in the reaction mechanism described above. The result obtained in this work supports this idea. The ionic species formed will attack \( \alpha \)-methylstyrene molecule, according to Eq. (2). This reaction may occur easily, influenced by the electron donating groups attached to the benzene ring of aryl group. The carbonium ion 1, formed by reaction expressed in Eq. (2), reacts with water to give the intermediate 2. As described above, the aryI groups rearrange to form substituted benzyl methyl ketone 3, expressed in Eq. (4). The aryI groups having electron donating groups should readily undergo rearrangement. These ideas are supported experimentally as shown in Fig. 6.

Further, effect of amount of substrate (\( \alpha \)-methylstyrene) on the reaction was studied. The results obtained are shown in Fig. 7. Data in Fig. 7 support the result shown in Fig. 5 from another point of view. That is, this reaction indicates that the stoichiometrical reaction of substrate(\( \alpha \)-methylstyrene) with oxidant(iodosylbenzene diacetate) gives the optimum yield, according to reaction schemes described above. From the results shown in Figs. 5 and 7, there may be a remote possibility that Eq. (1) or (2) is a rate-determining step of this reaction.

References

要 質

ヨードシルベンゼンジアセテートを用いた α-メチルステレンの酸化

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ペンジルメチルケトン（BMK）とその誘導体の有利な合成法について報告する。ヨードシルベンゼンジアセテート（IBD）を用いた α-メチルステレン（α-MS）の酸化について検討した。BMK の合成には、IBD が四酢酸鉛に比較してかなり優れた酸化剤であった。最適な実験条件下では、BMK の収率および選択率はそれぞれ 93% と 93% であった。この反応は硫酸存在下、酢酸-水混合溶媒中で効率的に進行した。置換 α-MS 誘導体の反応性について検討した結果、本反応はハメット則を満足し、ρ 値は -2.56 であった。フェニル基の転位を含む合理的な反応機構が提案された。

Keywords
Iodosylbenzene diacetate, Oxidation, α-Methylstyrene, Benzyl methyl ketone, Novel process, Reaction mechanism