HOMOLOGATION OF VICINAL POLYKETONE NETWORKS TO EPOXY KETONES WITH DIAZOMETHANE†

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Abstract – Admixture of vicinal di-, tri-, and tetraketones with ethereal diazomethane results in one-time methylene transfer to the less hindered face of the sterically most accessible and electron-deficient carbonyl group to deliver epoxy ketones in a highly selective manner unless ring strain effects contravene.

The epoxy ketone functional group is valued in organic synthesis because of the several reactive sites resident therein. Despite the breadth of chemical transformations to which this compound class has been subjected, their preparation has relied almost exclusively on the alkaline peroxidation of \( \alpha,\beta \)-unsaturated ketones.\(^{1,2} \) The oxygen atom of the oxirane ring is consequently introduced last. Occasions can be envisioned where insertion of the carbon atom in the final maneuver is desirable for stereochemical reasons or because the particular conjugated enone is notably prone to anionic polymerization.

Rather remarkably, the possibility of adding diazomethane to vicinal polycarbonyl functional groups has been only infrequently applied. Beyond this, the few early reports of the implementation of this reaction are hardly indicative of its latent synthetic potential or breadth.\(^3 \) As well, reports documenting the transformation of \( \alpha \)-keto esters such as 1 into 2 are limited.\(^4 \) For \( \alpha \)-dicarbonyl systems recognized to have an elevated enol content, \( O \)-methylated vinylogous esters typified by 4 are formed under similar conditions.\(^5 \)

\[ \begin{align*}
1 & \quad \begin{array}{c}
\text{R} \quad \text{OMe} \\
\text{O} \\
\text{O}
\end{array} \\
\text{(R = Ph, Ph\textsubscript{2}CH, 2-thienyl)} \\
\text{CH\textsubscript{2}N\textsubscript{2}} \quad \text{ether} \\
\text{(68-100%)} \\
2 & \quad \begin{array}{c}
\text{R} \quad \text{OMe} \\
\text{O} \\
\text{O}
\end{array}
\end{align*} \]

\[ \begin{align*}
3 & \quad \begin{array}{c}
\text{Br} \\
\text{OH}
\end{array} \\
\text{Br} \quad \text{OMe} \\
\text{O}
\end{align*} \]

\[ \begin{align*}
\text{CH\textsubscript{2}N\textsubscript{2}} & \quad \text{ether} \\
\text{(79%)}
\end{align*} \]

\[ \begin{align*}
4 & \quad \begin{array}{c}
\text{Br} \\
\text{OMe}
\end{array}
\end{align*} \]

†This paper is dedicated to Pierre Potier as we celebrate his 70th birthday and his many elegant contributions to the field of synthetic organic chemistry.
We now report on the general feasibility of adding diazomethane to vicinal polyketones \( R(CO)_nR' \) where \( n = 2-4 \), which reaction often results in one-time insertion of an oxiranyl carbon. A priori, the regioselectivity and \( \beta \)-facial stereoselectivity of this process can be expected to be controlled by steric factors and extendable to cyclic and open-chain substrates alike.

First to be explored were the acyclic systems (5-9) (Table I). In all five examples, the reactant was treated with approximately 10 equiv of ethereal diazomethane and allowed to stir overnight at room temperature. The co-addition of silica gel to the reaction mixture as in the case of 8 served to accelerate the conversion to product and enhance the yield of oxirane to some degree. As expected, the homologation of 7 was totally regioselective, with exclusive involvement of its aldehyde carbonyl.

The five cyclic \( \beta \)-diketones (10-14) selected for study (Table II) are all recognized to bypass measurable equilibration with their diosphenol tautomers. For 12 and 14, no prototropic shift is possible. In the first three examples, reaction proceeded smoothly to generate the anticipated epoxy ketones in good yield. The regiochemistry exhibited by 12 is clearly a consequence of prevailing steric shielding, as is the

<table>
<thead>
<tr>
<th>Table I. Acyclic systems(^a)</th>
<th>reactant</th>
<th>product</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>80(^b)</td>
</tr>
<tr>
<td>9</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>81(^c)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table II. Cyclic systems(^a)</th>
<th>reactant</th>
<th>product</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>53</td>
</tr>
<tr>
<td>11</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>69</td>
</tr>
<tr>
<td>12</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>77(^b)</td>
</tr>
<tr>
<td>13</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>92(^b,c)</td>
</tr>
<tr>
<td>14</td>
<td>( R(CO)R' )</td>
<td>( R(CO)OR' )</td>
<td>84(^c)</td>
</tr>
</tbody>
</table>

\(^a\)10 equiv. of \( \text{CH}_2\text{N}_2 \) in ether. \(^b\)SiO\(_2\) also present. \(^c\)\(^1\)H NMR (500 MHz, CDCl\(_3\)) \[ \begin{array}{l} 3.20 (s, 4 \text{ H}), 1.24 (s, 18 \text{ H}); ^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3) \end{array} \] \[ \begin{array}{l} 215.3, 74.0, 64.3, 42.8, 26.5. \end{array} \]
response of 13. Where 13 and 14 are concerned, the capture of CH$_2$N$_2$ is kinetically retarded because of the space demands enforced by their bicyclic architecture. For this reason, the yields of 15-17 should not be regarded as optimized under the generic conditions adopted herein. Beyond this, the experiment involving 14 demonstrates that the strain inherent in camphorquinone is such as to deter advancement of 18 to the epoxide. Instead, ring expansion to 19 operates, with subsequent $\text{O}$-methylation of both possible tautomers.$^6$

![Chemical diagram](image)

The aryl-fused reactants (20-22) follow the established pattern of behavior, although conversion to product occurs more sluggishly and with increased opportunity for unwanted side reactions (Table III). The regioselectivity exhibited by 21 conforms to that observed in its reaction with other nucleophilic species.$^7$

To understand better the scope of this reaction, we turned finally to the 1,2-cyclobutenedione class of reactants (Table IV). Although dimethyl squarate (25) proved to give relatively messy results, all three members of the 23-25 subset were transformed into the corresponding cyclopentene-1,3-diones. Like 14, therefore, ring strain issues did not allow for epoxide formation. However, unlike 14, the diketonic products did not react further with diazomethane, a result attributable to vanishing levels of enol content so as to avoid the development of destabilizing cyclopentadienone characteristics.

<table>
<thead>
<tr>
<th>Table III. Aryl-fused [(\text{\textregistered})]-diketones$^a$</th>
<th></th>
<th>Table IV. Cyclobutene-1,2-diones$^a$</th>
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<tbody>
<tr>
<td>reactant</td>
<td>product</td>
<td>yield, %</td>
</tr>
<tr>
<td><img src="image" alt="Chemical structure" /> 20</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>88$^b,c$</td>
</tr>
<tr>
<td><img src="image" alt="Chemical structure" /> 21</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>96$^{b,c}$</td>
</tr>
<tr>
<td><img src="image" alt="Chemical structure" /> 22</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>53$^c$</td>
</tr>
</tbody>
</table>

$^a$ See footnotes to Table II.

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In summary, CH$_2$N$_2$ has been shown to react readily with vicinal polyketones. The initial attack is followed by denitrogenation with ring closure to give an oxirane unless ring strain effects are present. Under the latter circumstances, ring expansion results to deliver cyclic 1,3-diketones. The latter may react with a second equivalent of diazomethane depending on structural features.

ACKNOWLEDGMENT
We thank Professor Rolf Gleiter for generously providing samples of 8 and 9.

REFERENCES AND NOTES