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A VERSATILE SYNTHESIS OF 3-SUBSTITUTED 5-ALKYL BUTYROLACTONES
VIA DYTROPIC REARRANGEMENT

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Abstract: Substituted acetic acid dianions are convertable to to 3,5-disubstituted butyrolactones, employing a dyotropic rearrangement as the key step.

The butyrolactone (dihydro-2(3H)-furanone) functionality is widespread throughout various natural product families,\(^1\) and also comprises an integral moiety in a large number of molecules with important pharmacological applications.\(^2\) Additionally, butyrolactones serve as versatile starting materials for other important compound classes, such as furans, cyclopentenones, etc.\(^3\) Thus, interest in general synthetic methods for construction of these rings has been widespread.

A large variety of approaches to substituted butyrolactones are available.\(^4\) The last step most usually entails the dehydration of the corresponding 3-hydroxy acids with the desired substituent groups already in place. An exception is lactones which bear alkyl groups in the alpha (3-) position, which are
accessible via alkylation of enolates available via deprotonation of butyrolactone with bases such as lithium diisopropylamide. Placement of substituents such as phenyl, phenoxy, methoxy, etc. which cannot be introduced via an enolate protocol is considerably more difficult.

We recently reported a new synthetic method for the preparation of spiro butyrolactones from cyclohexanecarboxaldehyde and substituted acetic acid derivatives. Due to the greater interest in and utility of monocyclic lactones, however, we deemed it important to pursue an ancillary study directed toward the synthesis of these molecules. This has resulted in the development of a method which allows facile access to a variety of 5-methyl butyrolactones, and should be similarly applicable to other 5-alkyl derivatives, which are substituted in the 3-position with groupings largely unavailable through direct functionalization of the parent lactone.

For the purposes of this study, propionaldehyde was chosen as the precursor since the resulting 5-methyl butyrolactones are not only more amenable to spectroscopic analysis but are also reported in the literature to a greater extent. The overall sequence is depicted in the Scheme, and the results are collected in the Table. To a solution of lithium diisopropylamide (2 eq) in tetrahydrofuran (−50°) was added a solution of the acetic acid derivative; a solution of propionaldehyde was then added, and the mixture was stirred for 16 hours. This reaction time was found to be essential to allow complete reaction and, more importantly, to
SUBSTITUTED ACETIC ACID DIANIONS

Scheme

RCH₂CO₂H \xrightarrow{1.2 \text{ LDA}} \xrightarrow{2. \text{C₂H₅CHO}} \text{RCH(OH)CO₂H} \xrightarrow{\text{PhSO₂Cl}} \text{RCH₂CO₂H} \xrightarrow{\text{MgBr₂}} \text{O₃C₅R}

Table

Yield data for the transformation of substituted acetic acid derivatives to 3,5-disubstituted butyrolactones

<table>
<thead>
<tr>
<th>Suffix</th>
<th>Acid</th>
<th>Yield of 1°</th>
<th>Yield of 2°</th>
<th>Yield of 3°</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>PhCH₂CO₂H</td>
<td>85.5</td>
<td>98.6</td>
<td>64.0</td>
</tr>
<tr>
<td>b</td>
<td>PhOCH₂CO₂H</td>
<td>78.8</td>
<td>62.4</td>
<td>72.3</td>
</tr>
<tr>
<td>c</td>
<td>PhSCH₂CO₂H</td>
<td>74.9</td>
<td>61.0</td>
<td>90.0</td>
</tr>
<tr>
<td>d</td>
<td>CH₃CH₂CH₂CO₂H</td>
<td>60.2</td>
<td>80.5</td>
<td>89.8</td>
</tr>
<tr>
<td>e</td>
<td>CH₃CO₂H</td>
<td>31.9</td>
<td>69.7</td>
<td>62.5</td>
</tr>
<tr>
<td>f</td>
<td>MeOCH₂CO₂H</td>
<td>13.8</td>
<td>61.8</td>
<td>83.3</td>
</tr>
</tbody>
</table>

a. All yields, while unoptimized, pertain to material purified as specified.
b. Recrystallized from chloroform.
c. Filtered through silica gel.
d. Recrystallized from hexane (if crystalline) or distilled (if oil).
maximize formation of the thermodynamically-favored threo diastereomer. Shorter times resulted in considerable contamination by the erythro isomer with attendant purification problems and subsequent lowering of yields. The hydroxy acids 1 were easily cyclized to afford the corresponding propiolactones 2 via treatment with benzenesulfonyl chloride/pyridine. Purification was effected by filtration through silica gel to remove color and polar impurities, since distillation was found to promote formation of alkenes via decarboxylation.

The propiolactones thus secured were treated with magnesium bromide etherate, resulting in a simultaneous lactone-ring expansion/sigma bond migration to afford the butyrolactones 3. In no cases was carbon migration observed, consistent with our earlier report. It appears that hydrogen migration is always the preferable reaction pathway, providing that the molecule is capable of adopting a conformation wherein the indicated lactone carbon-oxygen bond and a carbon-hydrogen bond on the pendant alkyl group are aligned in an anticoplanar fashion:

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{R} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Yields for the rearrangement were good to excellent and the products thus produced often analytically pure. The facile synthesis of 4,5-dihydro-5-methyl-3-(phenylthio)furan-2(3H)-one
(3c) is particularly noteworthy since it has served as the key intermediate in syntheses of both 6-angelicalactone \(^{10}\) and ancepsenolide.\(^ {11}\)

The preparation of the phenylthio derivative illustrates the method. The propiolactone 2c derived from 3-hydroxy-2-phenylthiopentanoic acid (453 mg, 2.06 mmol) was dissolved in anhydrous ether (5 mL) with stirring under nitrogen. Magnesium bromide etherate (1.06 g, 4.11 mmol) was added in one portion, and the light yellow mixture was stirred at room temperature for 10 hours. Water (15 mL) was cautiously added, and the product was isolated via ether extraction to afford 414 \(\mu\)g (91.3%) of butyrolactone 3c which displayed physical and spectral characteristics in accord with published data.\(^ {12}\)

We are actively extending this investigation to incorporate other acyclic aldehydes of widely varying structure in order to broaden the scope of this useful reaction and hopefully to define conditions under which carbon migration might occur.

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References


8. This behavior has been previously documented; cf. reference 7.


