EFFICIENT SYNTHESIS OF HYDROXYPHTHALIDES

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Abstract--- Naturally occurring hydroxyphthalides were synthesized via migration of double bond regio- and stereoselectively. Isomerization of E-isomer to Z-isomer easily occurred under acidic or basic conditions.

Several hydroxyphthalides such as senkyunolide-B (1), (Z)-3-butylidene-6,7-dihydroxyphthalide (2), (Z)-3-butylidene-7-hydroxyphthalide (3), and (Z)-3-butylidene-5-hydroxyphthalide (4) were recently isolated from the rhizome of *Ligusticum* or *Cnidium* species which were applied frequently to traditional Chinese medicines. In these compounds, although 1, 4 have already been synthesized, the synthesis of 4 has not been achieved so far. In this paper we wish to describe an efficient, regio- and stereoselective synthesis for these hydroxyphthalides (1-4) and isomerization of E-isomer to Z-isomer in this regard.

We have already reported the synthesis of 2 and the related compounds by the use of metallated phthalide in several steps. The stability of double bond of 3-alkylidene phthalides was examined to clarify the reaction pathway of the previous method which afforded a mixture of Z- and E-isomers. Although it is known that a isomerization between Z- and E-isomer occurs by an only irradiation of light, it was found that the isomerization of E-isomer...
to thermodynamically stable Z-isomer occurred smoothly with acid or base as shown in Table 1. In particular, 5E isomerized to 5Z with p-toluenesulfonic acid (PTSA) in quantitative yield. It was suggested that 5E isomerized to 5Z via an intermediate (6).

Table 1. Stability of E- and Z-isomers with acid or base

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time(h)</th>
<th>E/Z (ratio)a</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5E</td>
<td>DBU</td>
<td>Benzene</td>
<td>reflux</td>
<td>1</td>
<td>79 / 21</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>5E</td>
<td>DBU</td>
<td>Benzene</td>
<td>reflux</td>
<td>5</td>
<td>47 / 53</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>5E</td>
<td>PTSA</td>
<td>Benzene</td>
<td>reflux</td>
<td>1</td>
<td>0 / 100</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>5Z</td>
<td>DBU</td>
<td>Benzene</td>
<td>reflux</td>
<td>5</td>
<td>0 / 100</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>5Z</td>
<td>PTSA</td>
<td>Benzene</td>
<td>reflux</td>
<td>1</td>
<td>0 / 100</td>
<td>100</td>
</tr>
</tbody>
</table>

a) ratio of E/Z was determined by $^{1}$H-nmr analysis

Scheme 1

Z=Strong directed metallation group

Many different synthetic approaches to 3-alkylidenephthalides have already been reported, but they are not enough to prepare various hydroxyphthalides easily in regio- and stereoselective manner. Some of these methods lead to mixtures of E- and Z-isomers or 5- and 6-membered ring compounds and others are not useful in broad scope owing to difficulty of synthesis of the corresponding precursors.

We turned our attention to effective approach for the synthesis of hydroxyphthalides. Aryllithium intermediate (7) regioselectively generated with the aid of strong directed metallation group reacted with an unsaturated aldehyde to give lactone (8) which should be successively converted into migration product (10) as shown in Scheme 1.
Amides (15-18) were obtained from commercially available 11-14 by use of condensing agent such as diethyl chlorophosphate. Then lithiation of 15-18 with n-butyllithium in the presence of N,N,N',N'-tetramethyl-ethylenediamine (TMEDA), followed by reaction with trans-2-pentenal, hydrolysis with base, and cyclization by heat afforded 19-22. The only Z-isomer of 3-yldenephthalides (23-26)\textsuperscript{11} were stereoselectively obtained via migration of the double bond of 19-22 by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

3-Yldenephthalides (25, 26) of them were further converted to hydroxyphthalides (3, 4)\textsuperscript{11} by demethylation with boron tribromide\textsuperscript{10} (Scheme 2). Hydroxyphthalides (1, 2) have already been obtained from 23, 24 in the previous paper.\textsuperscript{4-5} The spectral data of these hydroxyphthalides were identical with those of natural products.

Scheme 2

\[
\begin{align*}
\text{R}^1\text{=OMe, R}^2\text{=R}^3\text{=R}^4\text{=H:} & \text{11} \\
\text{R}^1\text{=R}^2\text{=H, R}^3\text{=R}^4\text{=OMe:} & \text{12} \\
\text{R}^1\text{=R}^2\text{=R}^3\text{=H, R}^4\text{=OMe:} & \text{13} \\
\text{R}^1\text{=R}^2\text{=R}^3\text{=H, R}^4\text{=R}^2\text{=OMe:} & \text{14} \\
\text{R}^1\text{=OMe, R}^2\text{=R}^3\text{=R}^4\text{=H:} & \text{15 (79\%)} \\
\text{R}^1\text{=R}^2\text{=H, R}^3\text{=R}^4\text{=OMe:} & \text{16 (82\%)} \\
\text{R}^1\text{=R}^2\text{=R}^3\text{=H, R}^4\text{=OMe:} & \text{17 (73\%)} \\
\text{R}^1\text{=R}^3\text{=R}^4\text{=H, R}^2\text{=OMe:} & \text{18 (75\%)} \\
\text{R}^1\text{=OMe, R}^2\text{=R}^3\text{=R}^4\text{=H:} & \text{19 (55\%)} \\
\text{R}^1\text{=R}^2\text{=H, R}^3\text{=R}^4\text{=OMe:} & \text{20 (47\%)} \\
\text{R}^1\text{=R}^2\text{=R}^3\text{=H, R}^4\text{=OMe:} & \text{21 (70\%)} \\
\text{R}^1\text{=R}^3\text{=R}^4\text{=H, R}^2\text{=OMe:} & \text{22 (87\%)} \\
\end{align*}
\]

REFERENCES AND NOTES

11. 26: mp 56-57°C; ir (KBr) v max cm⁻¹: 1782 (C=O), 1692 (C=C); ¹H-nmr (CDCl₃) δ: 0.99 (3H, t, J=7.4 Hz), 1.55 (2H, t, J=7.4, 7.4 Hz), 2.44 (2H, dt, J=7.8, 7.4 Hz), 3.92 (3H, s), 5.59 (1H, t, J=7.8 Hz), 7.02 (1H, d, J=2.2 Hz), 7.02 (1H, dd, J=9.1, 2.2 Hz), 7.77 (1H, d, J=9.1 Hz), 25: Colorless oil (lit. bp 200-203°C); ir (KBr) v max cm⁻¹: 1776 (C=O), 1686 (C=C); ¹H-nmr (CDCl₃) δ: 0.98 (3H, t, J=7.4 Hz), 1.54 (2H, t, J=7.4, 7.4 Hz), 2.43 (2H, dt, J=7.8, 7.4 Hz), 4.00 (3H, s), 5.60 (1H, t, J=7.8 Hz), 6.90 (1H, d, J=8.2 Hz), 7.18 (1H, d, J=7.7 Hz), 7.59 (1H, dd, J=8.2, 7.7 Hz), 4: mp 117-119°C (lit. 69-70°C); ir (KBr) v max cm⁻¹: 1746 (C=O), 1682 (C=C); ¹H-nmr (CDCl₃) δ: 0.97 (3H, t, J=7.4 Hz), 1.54 (2H, t, J=7.4, 7.4 Hz), 2.42 (2H, dt, J=7.8, 7.4 Hz), 5.59 (1H, t, J=7.8 Hz), 7.02 (1H, dd, J=8.4, 2.1 Hz), 7.07 (1H, d, J=2.1 Hz), 7.10 (1H, br, exchangeable with D₂O), 7.76 (1H, d, J=8.4 Hz), 3: mp 75-76°C (lit. 69-70°C); ir (KBr) v max cm⁻¹: 1752 (C=O), 1686 (C=C); ¹H-nmr (CDCl₃) δ: 0.99 (3H, t, J=7.4 Hz), 1.55 (2H, t, J=7.4, 7.4 Hz), 2.44 (2H, dt, J=7.9, 7.4 Hz), 5.67 (1H, t, J=7.9 Hz), 6.91 (1H, d, J=8.2 Hz), 7.13 (1H, d, J=7.6 Hz), 7.45 (1H, br, exchangeable with D₂O), 7.54 (1H, dd, J=8.2, 7.6 Hz), The stereochemistry at C-8 of these compounds (23-26, 3, 4) was confirmed by the presence of NOE between the olefinic proton and the aromatic proton.

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