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Stereoselective Synthesis of 5-7 membered Cyclic Ethers by Deiodonative Ring-Enlargement Using Hypervalent Iodine Reagents

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Abstract: Stereoselective synthesis of 5-7 membered cyclic ethers was achieved by deiodonative ring-enlargement of cyclic ethers having an iodoalkyl substituent. The reaction took place readily under mild conditions using hypervalent iodine compounds and an acetoxy or a trifluoroacetoxy group was introduced into the rings depending on the hypervalent iodine reagent employed. The use of hexafluoroisopropanol (HFIP) as solvent is critical.

Keywords: Ring-enlargement, cyclic ether, hypervalent iodine compounds.

Introduction

Recently, we found that 5-7 membered fluoro cyclic ethers 2 can be stereoselectively prepared from 4-6 membered ones having an iodoalkyl substituent at the 2-position, 1, by the fluorinative ring-enlargement reaction induced by iodotoluene difluoride [1]. During our continued study of ring-enlargement reaction of cyclic ethers 1 using hypervalent iodine compounds, we found that cyclic ether having an acetoxy or a trifluoroacetoxy group, key intermediates for the synthesis of cyclic polyether natural compounds [2-5], can be stereoselectively synthesized by the reaction with (diacetoxyiodo)toluene (DIT) or [bis(trifluoroacetoxy)]iodobenzene (BTI).
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\[ \begin{align*}
1 \quad \text{ArIX}_2 & \quad \rightarrow \quad 3 \quad \text{X} = \text{F} \\
& \quad \text{X} = \text{OAc} \\
& \quad \text{X} = \text{OCOCF}_3
\end{align*} \]

Results and Discussion

When 2-(2-iodononyl)tetrahydrofuran (1a), obtained as a single stereoisomer by the iodocyclization reaction of (E)-4-methyl-4-tridecen-1-ol [6-12], was treated with DIT and acetic acid in a mixture of CH\(_2\)Cl\(_2\) and hexafluoroisopropanol (HFIP) at room temperature, the acetoxyalted tetrahydropyran derivative 3a was obtained as a main product, along with an acetoxy group-substituted tetrahydrofuran derivative 5a as a minor product (Table 1, Entries 2–4). The use of HFIP as solvent was critical [13] and without it, the reaction was sluggish (Entry 1). The best result was obtained by carrying out the reaction at room temperature in a 1:1 mixture of CH\(_2\)Cl\(_2\) and HFIP without AcOH, and 3a was isolated in 80% yield with high selectivity (3a:5a = 34:1) (Entry 5). A commercially available (diacetoxyiodo)benzene showed a similar reactivity as DIT (Entry 7). When BTI was used instead of DIT, the starting material 1a was consumed quickly, but a mixture of unidentifiable products was formed.

**Table 1.** Ring-enlargement reaction of 1a using DITA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>React Time (h)</th>
<th>Yield of 3a (%)b</th>
<th>3a : 5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl(_2) / HFIP (ml)</td>
<td>24</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>4 / 0</td>
<td>0.75</td>
<td>80</td>
<td>19 : 1</td>
</tr>
<tr>
<td>3</td>
<td>6 / 0.5</td>
<td>3.5</td>
<td>96</td>
<td>8 : 1</td>
</tr>
<tr>
<td>4</td>
<td>2 / 1</td>
<td>1</td>
<td>94</td>
<td>18 : 1</td>
</tr>
<tr>
<td>5c</td>
<td>2 / 1</td>
<td>1</td>
<td>96 (80)</td>
<td>34 : 1</td>
</tr>
<tr>
<td>6c,d</td>
<td>0 / 3</td>
<td>2.5</td>
<td>60</td>
<td>58 : 1</td>
</tr>
<tr>
<td>7c,e</td>
<td>2 / 1</td>
<td>0.5</td>
<td>(60)</td>
<td>72 : 1</td>
</tr>
</tbody>
</table>

aIf otherwise not mentioned, the reaction was carried out at room temperature using 1.1 eq of DIT and 5 eq of AcOH to 1a. bGC yield based on 1a and in parenthesis, isolated yield. cAcOH was not used. dThe reaction was carried out at 0 °C. e(Diacetoxyiodo)benzene was used instead of DIT.

The ring-enlargement reaction steroselectively proceeded to provide 3a as a single stereoisomer and its stereochemistry was determined from NOESY experiment.
As shown in Table 2, various 2,5-substituted tetrahydrofuran derivatives 1b-d could be converted to the corresponding 2,5-disubstituted tetrahydropyran derivatives 3b-d, which can be key intermediates for the synthesis of natural products [2]. The reaction proceeded stereospecifically and the trans- 3c or cis-2,5-disubstituted tetrahydropyran derivative 3d was obtained selectively from trans- 1c or the cis-disubstituted derivative 1d, respectively. A 7-membered cyclic ether, 3g, could also be prepared stereoselectively from a tetrahydropyran derivative, 1g, using DIT.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>React. Cond.</th>
<th>Product, Yield, %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct</td>
<td>RT, 1 h</td>
<td>80</td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td>5a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hex</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>1b</td>
<td>0 °C, 1 h</td>
<td>3b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3b</td>
</tr>
<tr>
<td>AcO</td>
<td>Hex</td>
<td>6</td>
</tr>
<tr>
<td>1c</td>
<td>0 °C, 2 h</td>
<td>3c</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5c</td>
</tr>
<tr>
<td>AcO</td>
<td>Hex</td>
<td>6</td>
</tr>
<tr>
<td>1d</td>
<td>0 °C, 1 h</td>
<td>3d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d</td>
</tr>
<tr>
<td>AcO</td>
<td>Hex</td>
<td>22</td>
</tr>
<tr>
<td>1e</td>
<td>RT, 1 h</td>
<td>45</td>
</tr>
<tr>
<td>CF₃COO</td>
<td>Hep</td>
<td>45</td>
</tr>
<tr>
<td>1f</td>
<td>RT, 1 h</td>
<td>50</td>
</tr>
<tr>
<td>CF₃COO</td>
<td>Hep</td>
<td>50</td>
</tr>
<tr>
<td>1g</td>
<td>0 °C, 0.5 h</td>
<td>3g</td>
</tr>
<tr>
<td>AcO</td>
<td>Hex</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Acyloxy ring-enlargement of cyclic ethers by DIT and BTI

*aIf otherwise not mentioned, the reaction was carried out using 1.1 eq of DIT to 1 in a mixture of CH₂Cl₂ and HFIP (1:2). *bIsolated yield based on 1. Yield of 5 was determined by GC. *cThe reaction was carried out using 2 eq of DIT in HFIP. *dBTI was used instead of DIT.
On the other hand, the reaction of 4-membered cyclic ethers 1e,f with DIT was sluggish and the starting materials remained even after 24 h. Ring-enlargement of 1e,f could be achieved by using BTI instead of DIT and the corresponding tetrahydrofuran derivatives 3e,f having a trifluoroacetoxy group could be obtained stereospecifically.

The reaction must proceed as follows: the oxidation of 1 by ArIX₂ gives an unstable hypervalent iodine intermediate 6 [14], which decomposes to an oxonium ion intermediate 7. The attack of an acyloxy group at the internal carbon of 7 provides the ring-enlarged product 3. On the other hand, an attack of an acyloxy group on the terminal carbon of 7 gives simple substituted product 5. As the bond cleavage between oxygen and the internal carbon in 7 generates a more stable carbocation, the formation of 3 takes place predominantly (Scheme 1).

**Scheme 1**

Conclusions

We have succeeded in the stereoselective synthesis of 5-7 membered cyclic ethers by deiodonative ring-enlargement of cyclic ethers having an iodoalkyl substituent using hypervalent iodine compounds. According to the method, an acyloxy group-substituted cyclic ethers could be readily prepared under mild conditions.

Acknowledgements

We are grateful to Central Glass Co., Ltd. for their donation of hexafluoroisopropanol (HFIP).

Experimental

**General**

¹H-NMR (400MHz) and ¹³C-NMR (100MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. DIT was
prepared from iodotoluene according to the literature [14]. BTI was obtained from Sigma-Aldrich Co. and used without further purification.

\((2R^*, 3S^*)\)-3-Acetoxy-2-octyl-3-methyltetrahydropyran \((3a)\). To DIT (370 mg, 1.1 mmol) in a mixture of HFIP (1 mL) and CH\(_2\)Cl\(_2\) (1 mL), was added a CH\(_2\)Cl\(_2\) solution (1 mL) of 1a (324 mg, 1 mmol) at room temperature and the mixture was stirred at the temperature for 1 h. Water (5 mL) and ether (5 mL) were added to the reaction mixture and the separated aqueous layer was extracted with ether (3 x 5 mL). The combined organic layer was washed with aqueous Na\(_2\)S\(_2\)O\(_3\), aqueous NaHCO\(_3\), and brine, successively. Then, the organic layer was dried over MgSO\(_4\), and concentrated under reduced pressure. Purification by column chromatography (silica gel / hexane-ether) gave 3a (217 mg, 80 %).

\[^1\text{H-NMR}\] \(\delta\): 3.94 – 3.90 (1H, m), 3.43 – 3.37 (1H, m), 3.29 (1H, d, J = 8.1 Hz), 2.65 – 2.62 (1H, m), 1.98 (3H, s), 1.77 – 1.52 (5H, m), 1.48 (3H, s), 1.28 (12H, brs), 0.88 (3H, t, J = 7.1 Hz); \[^{13}\text{C-NMR}\] \(\delta\): 14.1, 17.3, 22.4, 22.7, 24.3, 26.5, 28.8, 29.3, 29.6, 29.7, 31.9, 35.0, 63.8, 80.8, 82.1, 170.1; HRMS (EI) Calc. for C\(_{16}\)H\(_{31}\)O\(_3\) (M\(^++\)H) 271.2273. Found: 271.2281.

The formation of ca. 2% of 2-(2-acetoxynonyl)-2-methyltetrahydrofuran \((5a)\) was confirmed by GC. \[^1\text{H-NMR}\] \(\delta\): 4.91 (1H, dd, J = 10.5, 2.0 Hz), 3.89 – 3.84 (1H, m), 3.81 - 3.75 (1H, m), 2.08 (3H, s), 1.93 – 1.83 (3H, m), 1.64 – 1.41 (3H, m), 1.25 (12H, brs), 1.16 (3H, s), 0.88 (3H, t, J = 6.6 Hz); \[^{13}\text{C-NMR}\] \(\delta\): 14.1, 21.1, 22.5, 22.6, 26.0, 26.1, 29.2, 29.5, 29.6, 29.7, 31.8, 34.5, 68.3, 76.7, 83.7, 170.9; HRMS (EI) Calc. for C\(_{16}\)H\(_{31}\)O\(_3\) (M\(^++\)H) 271.2273. Found: 271.2258.

\((2R^*, 5R^*)\)-5-Acetoxy-2-hexyl-5-methyltetrahydropyran \((3b)\). \[^1\text{H-NMR}\] \(\delta\): 3.91 (1H, dd, J = 11.0, 2.4 Hz), 3.38 (1H, d, J = 11.0 Hz), 3.27 (1H, m), 2.38 – 2.32 (1H, m), 1.98 (3H, s), 1.59 (3H, s), 1.77 – 1.27 (13H, m), 0.88 (3H, t, J = 7.1 Hz); \[^{13}\text{C-NMR}\] \(\delta\): 14.1, 20.8, 22.5, 22.6, 25.6, 29.2, 29.3, 31.8, 34.4, 35.5, 73.9, 78.0, 78.3, 170.1; HRMS (EI) Calc. for C\(_{14}\)H\(_{26}\)O\(_3\) (M\(^++\)H) 242.1882. Found: 242.1878. The stereochemistry of 3b was determined by comparison of chemical shifts in \[^1\text{H-NMR}\] with reported data [15].

\((2R^*, 5R^*)\)-5-Acetoxy-2-hexyltetrahydropyran \((3c)\). \[^1\text{H-NMR}\] \(\delta\): 4.75 (1H, m), 4.00 (1H, ddd, J = 10.5, 4.9, 2.2 Hz), 3.25 – 3.12 (2H, m), 2.16 – 2.12 (1H, m), 2.03 (3H, s), 1.76 – 1.27 (13H, m), 0.88 (3H, t, J = 7.1 Hz); \[^{13}\text{C-NMR}\] \(\delta\): 14.1, 21.1, 22.2, 22.6, 25.6, 29.2, 29.3, 30.2, 31.8, 35.6, 68.5, 69.2, 77.5, 170.3; HRMS (EI) Calc. for C\(_{13}\)H\(_{24}\)O\(_3\) (M\(^++\)H) 228.1725. Found: 228.1709. The stereochemistry of 3c was determined by comparison of chemical shifts in \[^1\text{H-NMR}\] with reported data [16].

\((2R^*, 5S^*)\)-5-Acetoxymethyl-2-hexyltetrahydrofuran \((5c)\). \[^1\text{H-NMR}\] \(\delta\): 4.26 – 3.89 (2H, m), 2.10 (3H, s), 2.09 – 2.00 (2H, m), 1.65 -1.37 (14H, m), 0.88 (3H, t, J = 6.8 Hz).

\((2R^*, 5S^*)\)-5-Acetoxy-2-hexyltetrahydropyran \((3d)\). \[^1\text{H-NMR}\] \(\delta\): 4.80 (1H, brs), 4.01 (1H, d, J = 12.9 Hz), 3.58 (1H, dd, J = 12.9, 1.7 Hz), 3.31 – 3.26 (1H, m), 2.11 (3H, s), 2.09 – 1.94 (1H, m), 1.78 – 1.28 (13H, m), 0.88 (3H, t, J = 7.1 Hz); \[^{13}\text{C-NMR}\] \(\delta\): 14.1, 21.4, 22.6, 25.5, 26.7, 27.4, 29.3, 31.8, 36.2, 67.5, 69.7, 77.7, 170.9; HRMS (EI) Calc. for C\(_{13}\)H\(_{24}\)O\(_3\) (M\(^++\)H) 228.1725. Found: 228.1723. The stereochemistry of 3d was determined by comparison of its \[^1\text{H-NMR}\] chemical shifts with reported data [16].
(2R*, 5R*)-5-Acetoxymethyl-2-hexyltetrahydrofuran (5d). $^1$H-NMR $\delta$: 4.19 – 3.85 (2H, m), 2.09 (3H, s), 1.93 – 1.88 (2H, m), 1.68 – 1.37 (14H, m), 0.88 (3H, t, J = 6.8 Hz).

(2R*, 4R*)-4-Trifluoroacetoxy-2-heptyl-4-methyltetrahydrofuran (4e). $^1$H-NMR $\delta$: 3.94 (1H, d, J = 7.1 Hz), 3.56 (1H, dd, J = 7.3, 1.5 Hz), 2.26 (1H, ddd, J = 13.7, 6.6, 1.5 Hz), 1.79 (2H, dd, J = 13.9, 7.1 Hz), 1.53 (3H, s), 1.45 – 1.43 (2H, m), 1.28 (11H, brs), 0.88 (3H, t, J = 7.1 Hz); $^{13}$C-NMR $\delta$: 14.0, 21.8, 22.6, 25.5, 29.1, 29.3, 31.7, 35.6, 41.2, 69.5, 75.1, 79.6, 117.5, 120.4; HRMS (EI) Calc. for C$_{14}$H$_{24}$O$_3$F$_3$ (M$^+$) 296.1599. Found: 296.1603. The stereochemistry of 4e was determined from a NOESY experiment.

(2R*, 4S*)-4-Trifluoroacetoxy-2-heptyl-4-methyltetrahydrofuran (4f). $^1$H-NMR $\delta$: 4.19 – 4.13 (1H, m), 4.10 (1H, d, J = 7.1 Hz), 3.66 (1H, d, J = 7.1 Hz), 1.46 (3H, s), 1.78 – 1.27 (14H, m), 0.88 (3H, t, J = 7.1 Hz); $^{13}$C-NMR $\delta$: 14.1, 21.3, 22.6, 24.7, 29.1, 29.3, 31.7, 35.1, 39.9, 70.4, 74.2, 80.7, 117.3, 120.1; HRMS (EI) Calc. for C$_{14}$H$_{24}$O$_3$F$_3$ (M$^+$) 296.1599. Found: 296.1603. The stereochemistry of 4f was determined from a NOESY experiment.

6-Acetoxy-2-hexyl-6-methyloxepane (3g). $^1$H-NMR $\delta$: 4.24 (1H, d, J = 13.7 Hz), 3.36 – 3.30 (1H, m), 3.25 (1H, d, J = 13.7 Hz), 2.13 – 2.03 (2H, m), 2.01 (3H, s), 1.85 – 1.70 (2H, m), 1.40 (3H, s), 1.58 – 1.26 (12H, m), 0.88 (3H, t, J = 7.1 Hz); $^{13}$C-NMR $\delta$: 14.1, 20.5, 21.5, 22.5, 22.6, 26.1, 29.3, 31.8, 36.6, 36.7, 38.2, 77.2, 83.6, 85.7, 170.7; HRMS (EI) Calc. for C$_{15}$H$_{28}$O$_3$ (M$^+$) 256.2038. Found: 256.2038. Only a single stereoisomer was contained in 3g, however the identification of its stereochemistry failed.

References and Notes
