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

Title

Reagents

Author(s)
Abo, Tomohito; Sawaguchi, Masanori; Senboku, Hisanori; Hara, Shoji

Citation
Molecules, 10(1): 183-189

Issue Date
2005-01

Doc URL
http://hdl.handle.net/2115/15850

Type
article

File Information
MOLE10-1.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP
Stereoselective Synthesis of 5-7 membered Cyclic Ethers by Deiodonative Ring-Enlargement Using Hypervalent Iodine Reagents

Tomohito Abo, Masanori Sawaguchi, Hisanori Senboku and Shoji Hara*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan. Tel. +81-11-706-6556, Fax +81-11-706-6556.

*Author to whom correspondence should be addressed, e-mail: hara@org-mc.eng.hokudai.ac.jp

Received: 19 April 2004 / Accepted: 15 July 2004 / Published: 31 January 2005

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 iodonitrobenzene 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 (diacetoxiiodo)toluene (DIT) or [bis(trifluoroacetoxy)]iodobenzene (BTI).
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 CH₂Cl₂ and hexafluoroisopropanol (HFIP) at room temperature, the acetoxylated 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 CH₂Cl₂ 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.

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>React. Cond.</th>
<th>Product, Yield, %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Oct</td>
<td>RT, 1 h</td>
<td>3a AcO</td>
</tr>
<tr>
<td>1b Hex</td>
<td>0 °C, 1 h</td>
<td>3b AcO</td>
</tr>
<tr>
<td>1c Hex</td>
<td>0 °C, 2 h</td>
<td>3c AcO</td>
</tr>
<tr>
<td>1d Hep</td>
<td>0 °C, 1 h</td>
<td>3d AcO</td>
</tr>
<tr>
<td>1e Hep</td>
<td>RT, 1 h</td>
<td>4e CF3COO</td>
</tr>
<tr>
<td>1f Hep</td>
<td>RT, 1 h</td>
<td>4f CF3COO</td>
</tr>
<tr>
<td>1g Hex</td>
<td>0 °C, 0.5 h</td>
<td>3g AcO</td>
</tr>
</tbody>
</table>

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

\(^1\)H-NMR (400MHz) and \(^13\)C-NMR (100MHz) spectra were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, \(\delta\), 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 CH₂Cl₂ (1 mL), was added a CH₂Cl₂ 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 Na₂S₂O₃, aqueous NaHCO₃, and brine, successively. Then, the organic layer was dried over MgSO₄, and concentrated under reduced pressure. Purification by column chromatography (silica gel / hexane-ether) gave 3a (217 mg, 80 %). ¹H-NMR δ: 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); ¹³C=NMR δ: 14.1, 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 C₁₆H₃₁O₃ (M⁺+H) 271.2273. Found: 271.2281.

The formation of ca. 2% of 2-(2-acetoxynonyl)-2-methyltetrahydrofuran (5a) was confirmed by GC. ¹H-NMR δ: 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); ¹³C-NMR δ: 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 C₁₆H₃₁O₃ (M⁺+H) 271.2273. Found: 271.2258.

(2R*, 5R*)-5-Acetoxy-2-hexyl-5-methyltetrahydropyran (3b). ¹H-NMR δ: 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); ¹³C-NMR δ: 14.1, 20.8, 22.2, 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 C₁₄H₂₆O₃ (M⁺) 242.1882. Found: 242.1878. The stereochemistry of 3b was determined by comparison of chemical shifts in ¹H-NMR with reported data [15].

(2R*, 5R*)-5-Acetoxy-2-hexyltetrahydropyran (3c). ¹H-NMR δ: 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); ¹³C-NMR δ: 14.1, 21.1, 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 C₁₃H₂₄O₃ (M⁺) 228.1725. Found: 228.1709. The stereochemistry of 3c was determined by comparison of chemical shifts in ¹H-NMR with reported data [16].

(2R*, 5S*)-5-Acetoxymethyl-2-hexyltetrahydrofuran (5c). ¹H-NMR δ: 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). ¹H-NMR δ: 4.80 (1H, brs), 4.01 (1H, d, J = 12.9 Hz), 3.58 (1H, dd, J = 12.9, 1.7 Hz), 3.33 – 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); ¹³C-NMR δ: 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 C₁₃H₂₄O₃ (M⁺) 228.1725. Found: 228.1723. The stereochemistry of 3d was determined by comparison of its ¹H-NMR chemical shifts with reported data [16].
(2R*, 5R*)-5-Acetoxymethyl-2-hexyltetrahydrofuran (5d). 1H-NMR δ: 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). 1H-NMR δ: 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); 13C-NMR δ: 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 C14H24O3F3 (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). 1H-NMR δ: 4.19 – 4.13 (1H, m), 4.10 (1H, d, J = 7.1 Hz), 4.09 (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); 13C-NMR δ: 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 C14H24O3F3 (M+) 296.1599. Found: 296.1603. The stereochemistry of 4f was determined from a NOESY experiment.

6-Acetoxy-2-hexyl-6-methyloxepane (3g). 1H-NMR δ: 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); 13C-NMR δ: 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 C13H28O3 (M+) 256.2038. Found: 256.2038. Only a single stereoisomer was contained in 3g, however the identification of its stereochemistry failed.

References and Notes
