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).
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 acetoxylation of 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.

Table 1. Ring-enlargement reaction of 1a using DIT

| Entry | Solvent CH2Cl2 / HFIP (ml) | React Time (h) | Yield of 3a (%)b | 3a : 5a |
|-------|-----------------------------|----------------|------------------|---------|
| 1     | 4 / 0                       | 24             | 0                | —       |
| 2     | 4 / 2                       | 0.75           | 80               | 19 : 1  |
| 3     | 6 / 0.5                     | 3.5            | 96               | 8 : 1   |
| 4     | 2 / 1                       | 1              | 94               | 18 : 1  |
| 5c    | 2 / 1                       | 1              | 96 (80)          | 34 : 1  |
| 6cd   | 0 / 3                       | 2.5            | 60               | 58 : 1  |
| 7ce   | 2 / 1                       | 0.5            | (60)             | 72 : 1  |

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 stereoselectively 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.

| Substrate | React. Cond. | Product, Yield, % | Yield of 5 | the reaction was carried out using 2 eq of DIT in HFIP. 4BTI was used instead of DIT. |
|-----------|--------------|-------------------|------------|-----------------------------------------------------------------|
| 1a Oct | RT, 1 h | Oct | 80 | 2 | 45 | 5a |
| 1b Hex | 0 °C, 1 h | H | 76 | 3b |
| 1c Hex | 0 °C, 2 h | H | 63 | 3c | 5c |
| 1d Hex | 0 °C, 1 h | H | 45 | 3d | 5d |
| 1e Hep | RT, 1 h | 45 | 4e |
| 1f Hep | RT, 1 h | Hep | 50 | 4f |
| 1g Hex | 0 °C, 0.5 h | Hex | 55 | 3g |

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 ArIX$_2$ 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.

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Experimental

General

$^1$H-NMR (400MHz) and $^{13}$C-NMR (100MHz) spectra were recorded in CDCl$_3$ 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.

\((2R^*, 3S^*)-3\text{-Acetoxy}-2\text{-octyl}-3\text{-methyldihydropyran} \ (3a)\). To DIT (370 mg, 1.1 mmol) in a mixture of HFIP (1 mL) and \(\text{CH}_2\text{Cl}_2\) (1 mL), was added a \(\text{CH}_2\text{Cl}_2\) 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, \(J = 8.1 \text{ Hz}\)), 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, \(J = 7.1 \text{ Hz}\)); \(^{13}\text{C-NMR} \delta: 14.1, 17.3, 22.4, 22.7, 24.3, 26.5, 28.8, 29.3, 29.6, 29.7, 31.9, 35.0, 63.8, 80.8, 82.1, 170.1; \text{HRMS (EI) Calc. for C}_{16}\text{H}_{31}\text{O}_3 (M^+ + H) 271.2273. Found: 271.2281.\)

The formation of ca. 2% of \(2\text{-}(2\text{-acetoxynonyl})-2\text{-methyltetrahydrofuran} \ (5a)\) was confirmed by GC. \(^1\text{H-NMR} \delta: 4.91 (1H, dd, \(J = 10.5, 2.0 \text{ Hz}\)), 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, \(J = 6.6 \text{ Hz}\)); \(^{13}\text{C-NMR} \delta: 14.1, 21.1, 22.5, 22.6, 26.0, 26.1, 29.2, 29.5, 29.6, 29.7, 31.8, 34.5, 68.3, 76.7, 83.7, 170.9; \text{HRMS (EI) Calc. for C}_{16}\text{H}_{31}\text{O}_3 (M^+ + H) 271.2273. Found: 271.2258.\)

\((2R^*, 5R^*)-5\text{-Acetoxy}-2\text{-hexyl}-5\text{-methyltetrahydropyran} \ (3b)\). \(^1\text{H-NMR} \delta: 3.91 (1H, dd, \(J = 11.0, 2.4 \text{ Hz}\)), 3.38 (1H, d, \(J = 11.0 \text{ Hz}\)), 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, \(J = 7.1 \text{ Hz}\)); \(^{13}\text{C-NMR} \delta: 14.1, 20.8, 22.2, 22.6, 25.6, 29.2, 29.3, 31.8, 34.4, 35.5, 73.9, 78.0, 78.3, 170.1; \text{HRMS (EI) Calc. for C}_{14}\text{H}_{26}\text{O}_3 (M^+) 242.1882. Found: 242.1878. \) The stereochemistry of 3b was determined by comparison of chemical shifts in \(^1\text{H-NMR} \) with reported data [15].

\((2R^*, 5R^*)-5\text{-Acetoxy}-2\text{-hexyltetrahydropyran} \ (3c)\). \(^1\text{H-NMR} \delta: 4.75 (1H, m), 4.00 (1H, ddd, \(J = 10.5, 4.9, 2.2 \text{ Hz}\)), 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, \(J = 7.1 \text{ Hz}\)); \(^{13}\text{C-NMR} \delta: 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; \text{HRMS (EI) Calc. for C}_{13}\text{H}_{24}\text{O}_3 (M^+) 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].

\((2R^*, 5S^*)-5\text{-Acetoxymethyl}-2\text{-hexyltetrahydropyran} \ (5c)\). \(^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, \(J = 6.8 \text{ Hz}\)).

\((2R^*, 5S^*)-5\text{-Acetoxy}-2\text{-hexyltetrahydropyran} \ (3d)\). \(^1\text{H-NMR} \delta: 4.80 (1H, brs), 4.01 (1H, d, \(J = 12.9 \text{ Hz}\)), 3.58 (1H, dd, \(J = 12.9, 1.7 \text{ Hz}\)), 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, \(J = 7.1 \text{ Hz}\)); \(^{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; \text{HRMS (EI) Calc. for C}_{13}\text{H}_{24}\text{O}_3 (M^+) 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 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). $^1$H-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); $^{13}$C-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 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 δ: 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 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 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 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); $^{13}$C-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 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

1. Inagaki, T.; Nakamura, Y.; Sawaguchi, M.; Yoneda, N.; Ayuba, S.; Hara, S. *Tetrahedron Lett.* 2003, *44*, 4117-4119.
2. Nakata, T.; Nomura, S.; Matsukura, H.; *Tetrahedron Lett.* 1996, *37*, 213-216.
3. Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* 1997, *38*, 5545-5548.
4. Hori, N.; Nagasawa, K.; Shimizu, T.; Nakata, T. *Tetrahedron Lett.* 1999, *40*, 2145-2148.
5. Takahashi, S.; Fujisawa, K.; Sakairi, N.; Nakata, T. *Heterocycles* 2000, *53*, 1361-1370.
6. Amouroux, R.; Gerin, B.; Chastrette, M. *Tetrahedron Lett.* 1982, *23*, 4341-4344.
7. Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* 1988, 862-868.
8. Brunel, Y.; Rousseau, G. *J. Org. Chem.* 1996, *61*, 5793-5800.
9. Conti, P.; Dallanoce, C.; Amici, M. D.; Micheli, C. D.; Carrea, G.; Zambianchi, F. *Tetrahedron: Asymmetry* 1998, *9*, 657-665.
10. Cossy, J.; Tresnard, L.; Belotti, D.; Pardo, D. G. *Tetrahedron Lett.* 2001, *42*, 251-254.
11. Knight, D. W.; Staples, E. R. *Tetrahedron Lett.* 2002, *43*, 6771-6773.
12. (a) Macdonald, T. L.; Narasimhan, N. *J. Org. Chem.* 1985, *50*, 5000-5001; (b) Sawaguchi, M.; Hara, S.; Nakamuar, Y.; Ayuba, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron* 2001, *57*, 3315-3319.
13. As for the role of HFIP as co-solvent, see: Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.* **1995**, *60*, 2320-2321.

14. Sharefkin, J. G.; Saltzmann, H. *Org. Synth., Coll. Vol. 5*, **1973**, 660-663.

15. Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416-2423.

16. Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 8133-8144.

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