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Fluorinative ring-expansion of cyclic ethers using *p*-iodotoluene difluoride. Stereoselective synthesis of fluoro cyclic ethers

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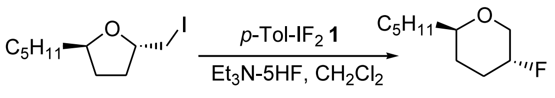
Abstract—Fluorinated five- to seven-membered cyclic ethers were stereoselectively synthesized from four- to six-membered cyclic ethers having an iodoalkyl substituent by fluorinative ring-expansion reaction using *p*-iodotoluene difluoride. © 2003 Elsevier Science Ltd. All rights reserved.

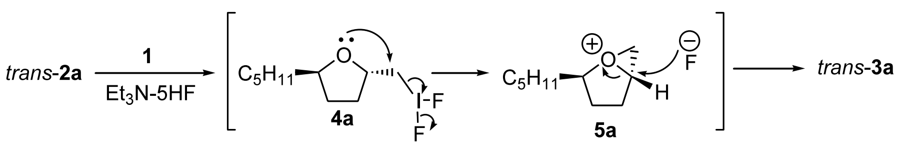
Considerable efforts have been expended towards the stereoselective synthesis of fluorinated cyclic ethers because their derivatives such as fluoro sugars have been used in probing biochemical mechanisms and fluoro nucleosides are expected as anti-HIV agents.[1] The fluorinated cyclic ethers had been synthesized by the cyclization of fluoro alcohols[2] or fluorination of cyclic ethers.[3] However, these methods involve the problems of stereoselectivity or require a multi-step process. We wish to report here a new methodology for the synthesis of fluorinated cyclic ethers, which includes fluorinative ring-expansion reaction using *p*-iodotoluene difluoride (**1**).[4] The starting cyclic ether **2a** can be prepared by iodocyclization of 1-decen-5-ol as a mixture of stereoisomers,[5] and was used for the reaction with **1** in the presence of Et_3N–5HF.[6] The reaction was completed in 1 h at room temperature and a ring-enlarged fluorinated cyclic ether **3a** was obtained as a mixture of two stereoisomers. The stereochemistry of each isomer could be determined from ^{1}H NMR. A large coupling value ($J=39.4$ Hz) between F and H-6 in the minor product indicates that the fluorine occupies an axial position and the minor isomer has *cis* stereochemistry.[8,9] In order to confirm the stereoselectivity of the reaction, the major isomer of **2a**, its sterochemistry was identified to be *trans*,[10] was separated and applied to the reaction with **1**. From *trans*-**2a**, only *trans*-**3a** was selectively obtained and, therefore, the reaction was shown to proceed stereoselectively (Eq. (1)).[12]



trans-**2a** *trans*-**3a** (1)

This selectivity can be explained by the following mechanism: the oxidation of **2a** with **1** gives an unstable hypervalent iodine intermediate (**4a**), which decomposes quickly to provide the oxonium ion (**5a**). A fluoride ion attacks **5a** through an S_N2 manner to give *trans*-**3a** stereoselectively (Scheme 1).[13]

Various fluorinated six-membered cyclic ethers (**3a**–**h**) were prepared from the five-membered starting materials (**2a**–**h**) as shown in Table 1 (entries 1–8). The fluorinative ring-expansion reaction from four to five (entries 9–11)[14] and from six to seven (entry 12) also took place.



Scheme 1.

Keywords: ethers; halogenation; hypervalent elements; oxidation.

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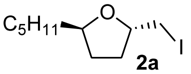
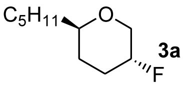
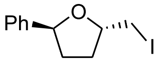
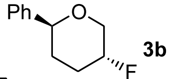
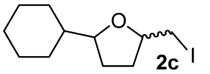
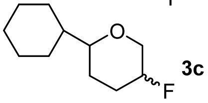
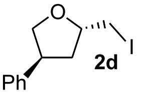
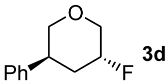
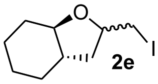
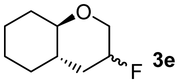
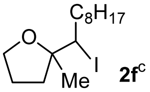
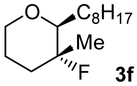
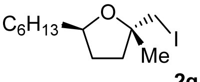
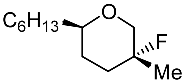
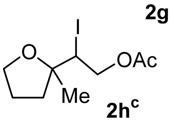
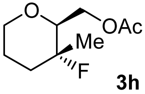
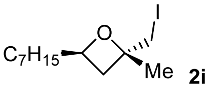
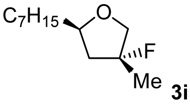
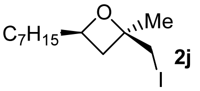
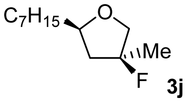
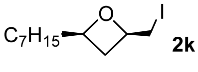
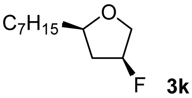
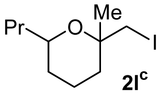
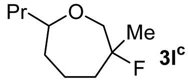
Table 1. Fluorinative ring-expansion reaction of cyclic ethers using **1**

Entry	substrate, **2**[a]	React. Time (h)	Product, **3**[a]	Yield, %[b]
1	 **2a**	1	 **3a**	70
2	 **2b**	2	 **3b**	66
3	 **2c** (trans : cis = 77 : 23)	2	 **3c** (trans : cis = 78 : 22)	65
4	 **2d**	3	 **3d**	66
5	 **2e**	1	 **3e**	63
6	 **2f**[c]	2	 **3f**	87
7	 **2g**	1	 **3g**	77
8	 **2h**[c]	1	 **3h**	62
9	 **2i**	1	 **3i**	88
10	 **2j**	1	 **3j**	86
11	 **2k**	1	 **3k**	57
12	 **2l**[c]	1	 **3l**[c]	50

a) Stereochemistry was determined from coupling constant in NMR and NOESY. b) Isolated yield based on **2** used. c) A single isomer. its stereochemistry was undetermined.

References

1. (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley: New York, 1991; (b) Hiyama, T. *Organofluorine Compounds*; Springer: Berlin, 2000.
2. (a) Hager, M. W.; Liotta, D. C. *Tetrahedron Lett.* **1992**, *33*, 7083–7086; (b) Nikitenko, A. A.; Arshava, B. M.; Mikerin, I. E.; Raifeld, Y. E. *Tetrahedron Lett.* **1992**, *33*, 7087–7088; (c) Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546–7547; (d) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 3443–3446; (e) Davis, F. A.; Qi, H.; Sundarababu, G. *Tetrahedron* **2000**, *56*, 5303–5310; (f) Mima, K.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *J. Fluorine Chem.* **2002**, *115*, 55–65.

3. Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197 and references cited therein.
4. Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, 1802–1803.
5. (a) Amouroux, R.; Gerin, B.; Chastrette, M. *Tetrahedron Lett.* **1982**, *23*, 4341–4344; (b) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862–868; (c) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793–5800; (d) Conti, P.; Dallanoce, C.; Amici, M. D.; Micheli, C. D.; Carrea, G.; Zambianchi, F. *Tetrahedron: Asymmetry* **1998**, *9*, 657–665; (e) Cossy, J.; Tresnard, L.; Belotti, D.; Pardo, D. G. *Tetrahedron Lett.* **2001**, *42*, 251–254; (f) Knight, D. W.; Staples, E. R. *Tetrahedron Lett.* **2002**, *43*, 6771–6773.
6. Addition of Et_3N–5HF is critical and without it, the reaction is sluggish. As for the role of Et_3N–5HF, see Ref. 7.
7. Sawaguchi, M.; Hara, S.; Nakamura, Y.; Ayuba, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron* **2001**, *57*, 3315–3319.
8. *cis*-**3a**: ^{1}H NMR (400 MHz) δ 4.58 (1H-5, d, $J_{\mathrm{F,H}} = 48.6$ Hz), 4.12 (1H-6eq, dd, $J_{\mathrm{H,F}} = 13.2$ Hz, $J_{\mathrm{H\text{-}6eq,H\text{-}6ax}} = 13.2$ Hz), 3.56 (1H-6ax, dd, $J_{\mathrm{H,F}} = 39.4$ Hz, $J_{\mathrm{H\text{-}6ax,H\text{-}6eq}} = 13.2$ Hz), 3.29 (1H-2, brs), 2.17–2.09 (1H, m), 1.80–1.28 (11H, m), 0.89 (3H, t, $J = 7.0$ Hz).
9. Card, P. J. *J. Org. Chem.* **1983**, *48*, 393–395.
10. The stereochemistry of each isomer of **2a** was determined from the chemical shift of their ^{1}H NMR spectra. The signals of H-2 and H-5 of the *trans*-isomer appear at lower fields than that of *cis*-isomers in 2,5-disubstituted tetrahydrofurans.[11]
11. Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Am. Chem. Soc.* **2000**, *122*, 11348–11357.
12. To a CH_2Cl_2 solution (2 ml) of *trans*-**2a** (282 mg, 1 mmol) in a Teflon™ vessel was added a mixture of Et_3N–5HF (2 ml) and **1** (333 mg, 1.3 mmol) at room temperature and the reaction mixture was stirred at room temperature for 1 h. (**CAUTION**: Although Et_3N–5HF is less corrosive than HF itself, it is recommended to use rubber gloves.) Then the reaction mixture was poured into water (3 ml) and the separated aqueous layer was extracted three times with CH_2Cl_2 (3 ml). The combined organic layer was washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and then brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography (silica gel/hexane–ether) gave *trans*-**3a** in 70% yield: IR (neat) 2933, 2858, 1101, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63–4.43 (1H-5, dm, $J_{\mathrm{F,H}} = 48.8$ Hz), 4.11–4.07 (1H-2, m), 3.30–3.19 (2H, m), 2.26–2.18 (1H, m), 1.83–1.77 (1H, m), 1.68–1.28 (10H, m), 0.88 (3H, t, $J = 6.9$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$) -188.02 to -187.83 (1F, m); HRMS calcd for $C_{10}H_{19}OF$: 174.1420, Found: 174.1409.
13. As for the ring-enlargement reaction of cyclic ethers through the oxonium ion as **5a**, see: (a) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230–2240; (b) Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213–216; (c) Hori, N.; Nagasawa, K.; Shimizu, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2145–2148.
14. Stereochemistry of **3i** and **3j** was determined from NOE spectra. NOE was observed between H-2 and Me group on a ring in **3j**. Stereochemistry of **3k** was determined from the comparison of its ^{1}H NMR with that of **3j**.