

The Stereoselectivities of Halocyclization of γ -Furanyloxy- and γ -Pyranyloxy-alkenes to 2,5-Disubstituted Tetrahydrofurans

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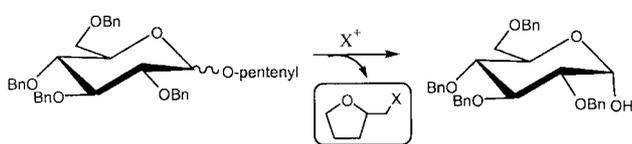
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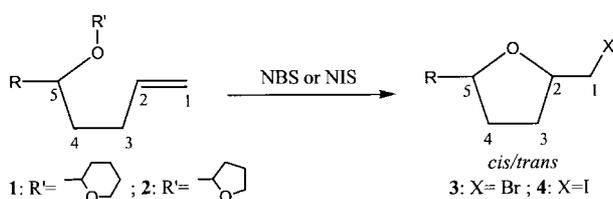
Methodologies based on the electrophilic halocyclization of γ -unsaturated alcohols to tetrahydrofurans (THFs), which are widely occurring sub-units in several classes of natural products, have been well established over the few decades.^{1,2} As an example, iodocyclizations of γ -hydroxyalkenes to substituted THFs were fully investigated by Bartlett *et al.*, in which they used benzyloxy derivatives to obtain 2,5-substituted THFs with high *cis* stereoselectivities.³ Recently, Fraser-Reid *et al.* reported that 4-pentenyl acetal moiety can be hydrolyzed by the treatment with halonium (X^+) species to produce 2-(halomethyl)furan from the *n*-pentenyloxy moiety (Scheme 1).^{4,5}

On the basis of these results, one can apply to the synthetic methodology for furan derivatives using the halocyclization of acetal derivatives of γ -hydroxyalkenes.⁶ Our studies in this area are aimed at obtaining 2,5-substituted tetrahydrofurans from any kinds of functionalized alkenes with reasonable stereoselectivities. Herein we report the diastereoselectivities of the halocyclization reaction of γ -tetrahydrofuranyloxy- and γ -tetrahydropyranyloxyalkenes to furans **3** and **4** using *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) as halonium sources (Scheme 2).

The acetals **1a-d** and **2a-d** were prepared from the reaction of corresponding alcohols, which were readily available from the reaction of 4-pentenal and the corresponding Grignard reagents, with 3,4-dihydro-2*H*-pyran or 2,5-dihydrofuran.⁷ The acetals **1** and **2** underwent cyclization using NBS



Scheme 1



1: R' = ; 2: R' =
 (a: R = Me, b: R = Et, c: R = *i*-Pr, d: R = *tert*-Bu)

Scheme 2

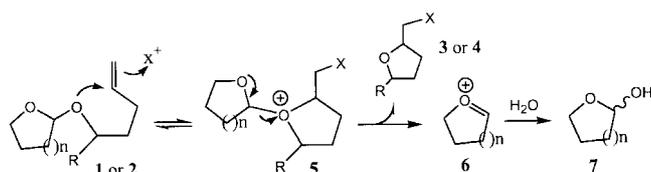
or NIS to give *cis/trans* isomeric mixtures of furans **3** or **4**. The ratios of *cis/trans* were estimated on the basis of the relative intensity of the two sets of ¹³C-NMR signals of the C-1 atoms. The accuracy of ¹³C-NMR method⁸ was counter-checked by ¹H-NMR (300 MHz) and GC-MS. The experimental results are shown in Table 1.

The results indicate that the cyclization of acetals **1** using NIS to furans shows better chemical yields and better *cis*-selectivities than those of NBS reaction (entries 1-7). The NIS cyclizations of acetals **2** exhibit no improved *cis* selectivities than those of acetals **1** (entries 4-6 and 8-10). The highest selectivity (>98%) was observed in the cyclization of acetal **2d** using NIS (entry 11). The acetal moiety of **1-2** presumed to display nucleophilic behavior leading to **5**, and then to liberate furan and **6**, which was trapped with water to give **7** (Scheme 3).^{9,10} The steric interaction between R group at C-5 and labile tetrahydrofuranyl moiety of intermediate **5** is developed, and results in forming the furan ring with *cis*-selectivity, which is similar to Bartlett's model.¹¹

Table 1. The results of halocyclization of **1-2** to tetrahydrofurans **3-4**

Entry	Reactant		Halonium source	Product	Yield (%) ^a	Ratios for <i>cis:trans</i>	
	R	R' ^c				by ¹ H	by ¹³ C ^b
1	1a	Me-	THP-	NBS	3a	40	58:42 54:46
2	1b	Et-	THP-	NBS	3b	54	64:36 64:36
3	1c	<i>i</i> -Pr-	THP-	NBS	3c	64	64:36 64:36
4	1a	Me-	THP-	NIS	4a	91	66:34 69:31
5	1b	Et-	THP-	NIS	4b	92	— 80:20
6	1c	<i>i</i> -Pr-	THP-	NIS	4c	93	76:24 80:20
7	1d	<i>t</i> -Bu-	THP-	NIS	4d	90	81:19 83:17
8	2a	Me-	THF-	NIS	4a	90	70:30 71:29
9	2b	Et-	THF-	NIS	4b	91	— 80:20 (79:21)
10	2c	<i>i</i> -Pr-	THF-	NIS	4c	92	84:16 88:12
11	2d	<i>t</i> -Bu-	THF-	NIS	4d	89	98:2 100:0 (98:2)
12	8	Et-	Glucosyl-	NIS	4b	35	— 78:22

^aIsolated yields of *cis/trans* isomeric mixtures. The isomers are inseparable by silica gel column chromatography. ^bThe ratios were obtained from the peak heights of ¹³C-NMR spectra of *cis/trans* isomeric mixtures (see ref. 8). The values of parenthesis are obtained from GC-MS of *cis/trans* mixtures. ^cTHP = tetrahydropyranyl-; THF = tetrahydrofuranyl-; Glucosyl = 2,3,4,6-tetra-*O*-benzyl- α and β -D-glucopyranosyl-.



Scheme 3

We next turned to investigate on the reaction of γ -glucopyranoxyalkene to introduce the bulkiness in the labile acetal moiety. However, the reaction of 3-glucopyranoxy-6-heptene¹² with NIS gives furan **4b** with moderate *cis*-selectivity (78 : 22, entry 12), although the bulkiness of glucopyranyl moiety is larger than tetrahydrofuranyl- and tetrahydropyranyl groups. We presumed that glucopyranyl moiety does not stay long enough for the effective steric role in intermediate **5** during the cyclization.

Characteristic chemical shifts of ¹H- and ¹³C-NMR, which are used for determining the ratios of *cis/trans* isomers, are shown in Table 2. For examples, the downfield chemical shifts of the ¹H-NMR signals of C6-protons of the major *cis* isomers of **3a** and **4a**, relative to the corresponding NMR signals in the minor *trans* isomers, argue for the *cis* geometry.¹³ Based on the ¹³C-NMR spectra of **3a** and **4a**, the upfield shifts for C1 are shown in the *cis* isomers relative to the *trans* isomers, which are general features to the other compounds.

In conclusion, the halocyclizations of acetals show moderate *cis*-diastereoselectivities (from 58 : 42 to 64 : 36 with NBS, from 69 : 31 to 88 : 12 with NIS) in forming 2,5-disubstituted furan ring with one exception (>98 : <2 for R=*tert*-Bu and R=THF with NIS). The downfield chemical shifts of the ¹H-NMR signals of C6-protons and the upfield shifts of the ¹³C-NMR spectra for C1 appear in the *cis* isomers relative to the *trans* isomers. Further studies aimed at

Table 2. Characteristic chemical shifts of ¹H- and ¹³C-NMR for *cis/trans* isomers of **3** and **4**^a

	¹ H-NMR ^b			¹³ C-NMR ^c
	C5-H	C6-H	C7-H	C-1
3a	–	1.22/1.19 (d, <i>J</i> = 6.04 Hz)	–	35.95/36.28
3b	3.8/3.9 (m)	–	0.89/0.87 (t, <i>J</i> = 7.4 Hz)	35.85/36.16
3c	3.5/3.6 (m)	–	0.91 & 0.83/0.90 & 0.81 (dd, <i>J</i> = 6.59 & 6.87/6.59 & 6.32 Hz)	35.70/36.12
4a	–	1.24/1.20 (d, <i>J</i> = 6.04 Hz)	–	10.98/11.36
4b	–	–	0.90/0.88 (t, <i>J</i> = 7.42 Hz)	10.94/11.26
4c	3.6/3.7 (m)	–	0.93 & 0.85/0.92 & 0.82 (dd, <i>J</i> = 6.87 & 6.86/6.32 & - Hz)	10.85/11.21
4d	3.6/3.7 (m)	–	0.87/0.85 (s)	10.62/11.14

^aChemical shifts for *cis/trans* isomers, relative to TMS (ppm). ^b300 MHz, measured in CDCl₃. ^c75 MHz, measured in CDCl₃.

extending the synthetic scopes and utilities of the halocyclization of γ -furanloxy- and γ -pyranloxyalkenes are continuing in our laboratory.

Experimental Section

General procedure for the cyclization of acetals using NBS: To a solution of acetal (1.0 mmol) in 1% aqueous acetonitrile (20 mL) was added *N*-bromosuccinimide (2.1 mmol) at room temperature. The reaction mixture was stirred at room temperature and was monitored by TLC and quenched with 10% aqueous sodium thiosulfate solution. The reaction mixture was extracted with diethyl ether (5 mL \times 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated to afford a crude product. The crude product showed a good spectrum in ¹H-NMR, and was further purified by silica gel column chromatography (ethyl acetate : *n*-hexane=1 : 6) to afford mixture of *cis/trans* isomers.

3a (*cis/trans*): *R*_f=0.63 (*n*-hexane : ethyl acetate = 6 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.27-3.96 (m, 2H, 2CH), 3.42-3.27 (m, 2H, CH₂-Br), 2.18-1.91 (m, 2H, CH₂), 1.82-1.67 (m, 1H, CH₂), 1.55-1.42 (m, 1H, CH₂), 1.22 (d, *J* = 6.04 Hz, 3H, CH₃ for *cis*), 1.19 (d, *J* = 6.05 Hz, 3H, CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 78.27, 76.57, 35.95, 32.71, 30.31, 21.19; (*trans* isomer) δ 77.76, 76.01, 36.28, 33.81, 31.13, 20.97.

3b (*cis/trans*): *R*_f = 0.56 (*n*-hexane : ethyl acetate = 6 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.23-4.06 (m, 1H, CH), 3.93 (m, 1H, CH for *trans*), 3.82 (m, 1H, CH for *cis*), 3.43-3.25 (m, 2H, CH₂-Br), 2.16-1.88 (m, 2H, CH₂), 1.81-1.33 (m, 4H, 2CH₂), 0.89 (t, *J* = 7.42 Hz, 3H, CH₃ for *cis*), 0.87 (t, *J* = 7.42 Hz, 3H, CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 81.94, 78.07, 35.85, 30.30, 30.02, 28.63, 10.16; (*trans* isomer) δ 81.46, 77.70, 36.16, 31.35, 30.86, 28.43, 10.09.

3c (*cis/trans*): *R*_f = 0.35 (*n*-hexane : ethyl acetate = 20 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.18-4.05 (m, 1H, CH), 3.68 (m, 1H, CH for *trans*), 3.58 (m, 1H, CH for *cis*), 3.43-3.22 (m, 2H, CH₂-Br), 2.14-1.50 (m, 5H, 2CH₂, CH), 0.91 (d, *J* = 6.59 Hz, 3H, CH₃ for *cis*), 0.90 (d, *J* = 6.59 Hz, 3H, CH₃ for *trans*), 0.83 (d, *J* = 6.87, 3H, CH₃ for *cis*), 0.81 (d, 6.32 Hz, 3H, CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 85.97, 77.93, 35.70, 32.98, 30.02, 27.993, 19.23, 18.25; (*trans* isomer) δ 85.45, 77.89, 36.12, 32.95, 31.14, 29.19, 19.20, 18.07.

General procedure for the cyclization of acetals using NIS: To a solution of acetal (1.0 mmol) in methylene chloride (20 mL) was added *N*-iodosuccinimide (2.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hrs and quenched with 10% aqueous sodium thiosulfate solution. The reaction mixture was treated by a standard aqueous work-up as described above.

4a (*cis/trans*): *R*_f = 0.33 (*n*-hexane : ethyl acetate = 20 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.23-3.89 (m, 2H, 2CH), 3.27-3.12 (m, 2H, CH₂-I), 2.23-1.92 (m, 2H, CH₂), 1.77-1.44 (m, 2H, CH₂), 1.24 (d, *J* = 6.05 Hz, 3H, CH₃ for *cis* iso-

mer), 1.20 (d, $J = 6.04$ Hz, 3H, CH₃ for *trans* isomer); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 78.48, 76.75, 32.83, 31.79, 21.37, 10.98; (*trans* isomer) δ 78.01, 76.10, 34.10, 21.09, 11.36.

4b (*cis/trans*): $R_f = 0.34$ (*n*-hexane : ethyl acetate = 20 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.08-3.80 (m, 2H, 2CH), 3.27-3.10 (m, 2H, CH₂-I), 2.20-1.89 (m, 2H, CH₂), 1.75-1.36 (m, 4H, 2CH₂), 0.90 (t, $J = 7.42$ Hz, 3H, CH₃ for *cis*), 0.88 (t, $J = 7.42$ Hz, 3H, CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 82.13, 78.27, 31.47, 30.41, 28.80, 10.94, 10.22; (*trans* isomer) δ 81.55, 77.96, 32.53, 31.63, 28.53, 11.26, 10.09; MS (m/e): (*cis* isomer) 240 (M⁺, 4), 211 (48), 113 (23), 99 (65), 83 (30), 81 (35), 57 (15), 55 (100), 53 (10); (*trans* isomer) 240 (M⁺, 6), 211 (63), 113 (29), 99 (97), 81 (44), 57 (16), 55 (100), 53 (8).

4c (*cis/trans*): $R_f = 0.40$ (*n*-hexane : ethyl acetate = 20 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.04-3.91 (m, 1H, CH), 3.73 (m, 1H, CH for *trans*), 3.61 (m, 1H, CH for *cis*), 3.28-3.09 (m, 2H, CH₂-I), 2.08-1.53 (m, 5H, 2CH₂, CH), 0.93 (d, $J = 6.87$ Hz, 3H, CH₃ for *cis*), 0.92 (d, $J = 6.32$ Hz, 3H, CH₃ for *trans*), 0.85 (d, $J = 6.86$ Hz, 3H, CH₃ for *cis*), 0.82 (d, 3H, CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 86.23, 78.18, 33.13, 31.48, 28.14, 19.29, 18.36, 10.85; (*trans* isomer) δ 85.59, 33.07, 32.81, 29.50, 19.23, 18.08, 11.21.

4d (*cis/trans*): $R_f = 0.35$ (*n*-hexane : ethyl acetate = 20 : 1); ¹H-NMR (CDCl₃, 300 MHz): δ 4.00-3.92 (m, 1H, CH), 3.74 (m, 1H, CH for *trans*), 3.60 (m, 1H, CH for *cis*), 3.29-3.08 (m, 2H, CH₂-I), 2.08-1.60 (m, 4H, 2CH₂), 0.87 (s, 9H, 3CH₃ for *cis*), 0.85 (s, 9H, 3CH₃ for *trans*); ¹³C-NMR (CDCl₃, 75 MHz): (*cis* isomer) δ 88.88, 78.07, 33.44, 31.52, 25.84, 25.70, 10.62; MS (m/e) (*cis* isomer) 268 (M⁺, 0.6), 212 (6), 211 (100), 210 (43), 183 (7), 127 (6), 83 (44), 71 (18), 57 (33), 55 (78), 53 (7).

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