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Reaction of homoallylic alcohols with $NaIO_4/NaHSO_3$ reagent—synthesis of alkyl substituted tetrahydrofuran derivatives

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Abstract

Treatment of homoallylic alcohols with $NaIO_4/NaHSO_3$ reagent in aqueous *t*-BuOH under mild conditions produced tetrahydrofuran derivatives together with iodohydrins in a stereospecific manner. The reaction pathways of the formation of tetrahydrofurans from *trans*- and *cis*-homoallylic alcohols were found to be different. The present method provides a new approach to various alkylated tetrahydrofuran derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: tetrahydrofuran; homoallylic alcohols; iodohydrins.

The tetrahydrofuran moiety is a constituent of a number of natural products and antibiotics.[1] Although several methods have been developed for the synthesis of tetrahydrofurans,[2] it is important to synthesize these compounds in a stereoselective way. Most reports on the synthesis of tetrahydrofurans from homoallylic alcohols involve iodine as a reagent and the reactions are carried out in the dark and without any water present.[2a–c]

Previously, we reported that $NaIO_4$ combined with an appropriate reducing agent such as $NaHSO_3$ ($NaIO_4/NaHSO_3$ reagent) generates in situ hypoiodous acid (IOH) and serves as an effective iodohydroxylation agent of alkenes.[3] In the course of our study to extend the scope of the $NaIO_4/NaHSO_3$ reagent in organic synthesis, we have found that this reagent can be applied to the stereoselective synthesis of tetrahydrofuran derivatives from homoallylic alcohols under mild conditions.

A typical reaction was carried out as follows: To a solution of *trans*-3-hexen-1-ol (**1a**) (3 mmol) and $NaIO_4$ (3.6 mmol) in a mixed solvent of *t*-BuOH (18 ml) and H_2O (6 ml) was added dropwise an aqueous solution (14 ml) of $NaHSO_3$ (7.2 mmol) over a period of ca. 30 min at

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50°C, and then the mixture was stirred at that temperature for 5 h. Reaction products were extracted three times with ethyl acetate, washed with aqueous $Na_2S_2O_3$ and dried over $MgSO_4$. After removal of the solvents in vacuo, products were isolated by column chromatography (silica gel, hexane:ethyl acetate = 10:1).

Table 1 shows the results for the reaction of various homoallylic alcohols with $NaIO_4$/$NaHSO_3$ reagent. The reaction of **1a** afforded *trans*-3-iodo-2-ethyltetrahydrofuran (**2a**) and *anti*-3-iodohexane-1,4-diol (**3a**) along with small amounts of unidentified polymeric products (Run 1). The structure of **2a** was determined by comparing its spectral data with that of literature values.[4] The reaction in CH_3CN gave almost the same results as that in *t*-BuOH (Run 2). The reaction in hexane afforded **2a** in 68% yield (Run 3). $NaIO_3$ and H_5IO_6 could also be used instead of $NaIO_4$ (Runs 4 and 5). On the other hand, *cis*-3-hexen-1-ol (**1b**) reacted with the $NaIO_4$/$NaHSO_3$ reagent under the same conditions as Run 1 to give *trans*-2-ethyl-3-hydroxytetrahydrofuran (**2b**) and *syn*-3-iodohexane-1,4-diol (**3b**) (Run 6). In contrast to **1a** having *trans* geometry where the furan **2a** was formed in preference to the iodohydrin **3a**, **1b** having *cis* geometry afforded preferentially iodohydrin **3b** rather than furan **2b**. Similarly, *cis*-3-nonen-1-ol (**1c**) gave *trans*-3-hydroxy-2-pentyltetrahydrofuran (**2c**) and *syn*-3-iodononene-1,4-diol (**3c**) in 55 and 40% yields, respectively (Run 8).

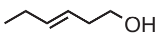
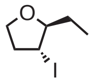
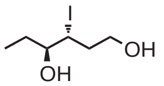
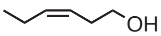
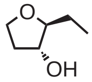
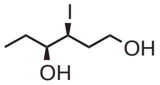
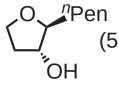
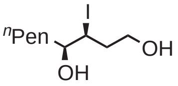
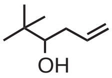
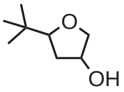
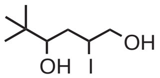
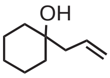
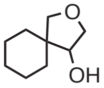
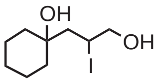
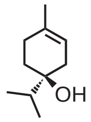
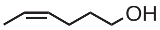
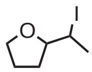
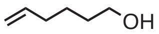
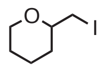
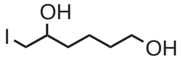
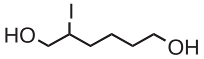
It is worth noting that these reactions took place in a stereospecific manner to form the corresponding furans and iodohydrins which subsequently undergo intramolecular cyclization to give rise to tetrahydrofurans. Scheme 1 shows plausible reaction paths for the formation of tetrahydrofurans **2a** and **2b** from **1a** and **1b**.

It is probable that the reaction is initiated by the attack of IOH generated from $NaIO_4$/$NaHSO_3$ reagent to the double bonds of **1a** and **1b** to afford the corresponding iodonium ion intermediates **A** and **B**, respectively. The formation of iodotetrahydrofuran **2a** from **1a** implies that the intramolecular cyclization of the iodonium ion **A** occurs in preference to the attack of a nucleophile like H_2O to the **A**. On the other hand, from **1b** having *cis* geometry, the hydroxytetrahydrofuran **2b** but not iodotetrahydrofuran was formed along with iodohydrin **3b**. This finding suggests that the attack of water to the iodonium ion intermediate **B** takes place in preference to the intramolecular cyclization of the **B** to form a mixture of **3b** and **3b′** which then cyclizes to **2b**. This may be due to the difficulty of the intramolecular cyclization of the hydroxy moiety to the *cis* iodonium ion intermediate **B** in comparison with the *trans* one **A**.

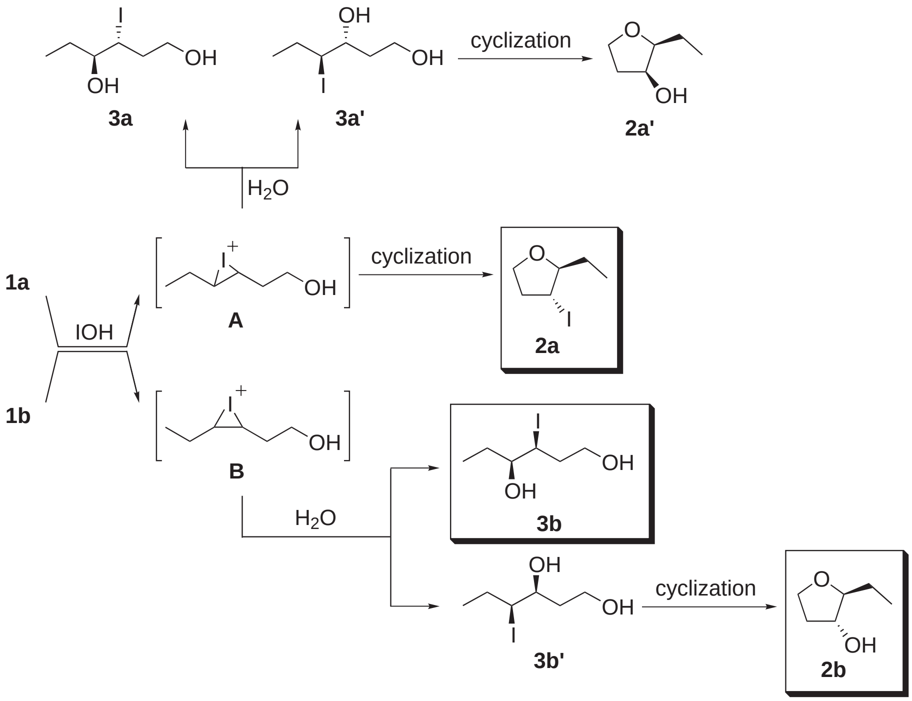
On the other hand, the reaction of homoallylic alcohol having a terminal double bond such as 4,4-dimethyl-1-hexen-4-ol (**1d**) with the $NaIO_4$/$NaHSO_3$ reagent resulted in 2-*tert*-butyl-4-hydroxytetrahydrofuran (**2d**) in 45% yield consisting of an approximate 1:1 stereoisomeric mixture. From 1-allyl-1-cyclohexanol (**1e**), spiro hydroxytetrahydrofuran derivative (**2e**) was obtained in 60% yield.

(+)-Terpinen-4-ol (**1f**) reacted with the $NaIO_4$/$NaHSO_3$ reagent to form *endo*-2-iodo-4-isopropenyl-1-methyl-7-oxabicyclo[2.2.1]heptane (**2f**) in 60% yield. Takahashi et al. reported that the photoreaction of **1f** with iodine (1.5 equiv.) in the presence of HgO (1.5 equiv.) leads to the **2f**.[5] Although a tetrahydropyran derivative was expected to be formed from 4-hexen-1-ol (**1g**), tetrahydrofuran derivative, 2-(1-iodoethyl)tetrahydrofuran (**2g**),[6] was formed. This indicates that the intramolecular cyclization of an iodonium ion intermediate generated in situ from **1g** takes place in preference to the attack of water leading to the corresponding iodohydrin **3g**. Similarly, the reaction of 5-hexen-1-ol (**1h**) with $NaIO_4$/$NaHSO_3$ gave 2-(1-iodomethyl)tetrahydropyran (**2h**)[7] as a major product along with small amounts of iodohydrins, 6-iodohexane-1,5-diol (**3h**) and 5-iodohexane-1,6-diol (**3h′**).

Table 1
Reaction of homoallylic alcohols and other alkenyl alcohols with $NaIO_4/NaHSO_3$ reagent$^{a)}$

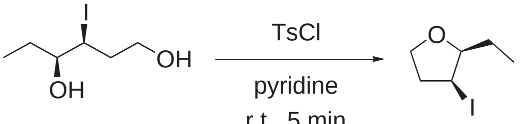
Run	Substrate	Solv.	Conv. / %	Product (Yield / %) $^{b)}$	
1	 **1a**	*t*-BuOH	85	 **2a** (56)	 **3a** (2)
2	**1a**	CH_3CN	89	**2a** (61)	**3a** (3)
3	**1a**	*n*-C_6H_{14}	94	**2a** (68)	**3a** (5)
4 $^{c)}$	**1a**	*n*-C_6H_{14}	99	**2a** (66)	**3a** (<1)
5 $^{d)}$	**1a**	*t*-BuOH	86	**2a** (59)	**3a** (6)
6	 **1b**	*t*-BuOH	99	 **2b** (42)	 **3b** (55)
7 $^{c)}$	**1b**	*n*-C_6H_{14}	96	**2b** (31)	**3b** (35)
8	 **1c**	*t*-BuOH	99	 **2c** (55)	 **3c** (40)
9	 **1d**	CH_3CN	99	 **2d** (45)	 **3d** (<5)
10	 **1e**	CH_3CN	99	 **2e** (60)	 **3e** (<5)
11	 **1f**	CH_3CN	93	 **2f** (60)	
12	 **1g**	CH_3CN	87	 **2g** (63)	
13	 **1h**	CH_3CN	83	 **2h** (48)	 **3h** (19)  **3h'** (7)

a) Substrate was added to the aqueous solution of organic solvent containing 1.1 or 1.2 equiv. of $NaIO_4$ followed by 2.2 or 2.4 equiv. of aqueous $NaHSO_3$ solution which was dropped slowly with a separatory funnel while stirring vigorously. b) Determined by GLC. c) $NaIO_3$ was used instead of $NaIO_4$. d) H_5IO_6 was used instead of $NaIO_4$.



Scheme 1. Plausible reaction paths for reactions of **1a** and **1b** with $NaIO_4/NaHSO_3$

It is important to convert the resulting iodohydrins into tetrahydrofuran derivatives. Hence the *syn*-3-iodohexane-1,4-diol **3b** was treated with tosylchloride in pyridine at room temperature for 5 min to give *cis*-2-ethyl-3-iodotetrahydrofuran (**4**)[4] in good yield (Eq. (1)). Thus, *cis*-homoallylic alcohol can also be converted into *cis* tetrahydrofuran derivative **4**.



3b → **4** 71% (1)

In conclusion, we have extended the synthetic utility of the $NaIO_4/NaHSO_3$ reagent which generates hypoiodous acid 'IOH' in aqueous solution. The present reaction provides an alternative approach to tetrahydrofuran derivatives from homoallylic alcohols in a stereospecific manner under mild conditions.

Spectral data: **2b**: δ_H 0.98 (t, 3H, $J=7.3$ Hz), 1.51 (two qd-like, 2H, $J=7.3$ Hz), 1.80 (brs, 1H), 1.83–1.89 (m, 1H), 2.08–2.17 (m, 1H), 3.63 (td-like, 1H, $J=2.9$, 6.6 Hz), 3.91–3.95 (m, 2H), 4.09 (dt-like, 1H, $J=2.9$, 6.2 Hz); δ_C 10.2, 26.4, 35.2, 66.1, 75.9, 87.8; IR 3380, 2963, 2963, 2928, 2877, 1682, 1462, 1096, 1059 cm^{-1}. **2c**: δ_H 0.82 (t, 3H, $J=6.6$ Hz), 1.18–1.42 (m, 8H), 1.78 (dddd-like, 1H, $J=2.9$, 4.0, 6.2, 12.8 Hz), 2.04 (dddd-like, 1H, $J=6.2$ Hz), 2.43 (brs, 1H), 3.61 (ddd-like, 1H, $J=2.9$ Hz), 3.80–3.89 (m, 2H), 3.98 (ddd-like, 1H, $J=2.9$, 2.9, 6.6 Hz); IR 3387, 2930, 2859, 1466, 1099, 993 cm^{-1}. **2d**: δ_H 0.89 (s, 9H), 1.73–1.85 (m, 2H), 2.14 (brs, 1H), 3.74 (ddd-like, 1H, $J=1.5$, 1.5, 9.6 Hz), 3.88 (dd, 1H, $J=4.0$, 9.9 Hz), 3.91 (dd, 1H, $J=6.4$, 9.9 Hz), 4.47 (br-dd-like, 1H); δ_C 25.6, 33.6, 36.1, 72.8, 75.8, 85.9; IR 3385, 2955, 2869, 1458, 1364, 1062, 984 cm^{-1}; (another isomer) δ_H 0.93 (s, 9H), 1.56–1.64 (m, 1H), 2.16 (ddd-like, 1H, $J=7.3$, 7.3, 14.7 Hz), 3.50 (dd-like, 1H, $J=7.7$, 8.4 Hz), 3.66 (dd, 1H, $J=4.4$, 9.9 Hz), 3.79 (ddd-like, 1H, $J=1.5$, 2.2, 9.9 Hz), 4.41 (m, 1H); δ_C 25.7, 33.2, 36.6, 72.2, 75.3, 87.1; IR 3389, 2926, 2855, 1470, 1366, 1059 cm^{-1}. **2e**: δ_H 1.26–2.18 (m, 11H), 1.95 (dd, 1H, $J=6.6$, 13.6 Hz), 2.10 (brs, 1H), 3.78 (dd, 1H, $J=3.7$, 9.9 Hz), 3.90 (dd, 1H, $J=4.4$, 9.9 Hz), 4.43–4.47 (m, 1H); δ_C 23.5, 23.8, 25.4, 37.1, 38.1, 46.0, 72.9, 73.4, 82.7; IR 3417, 2931, 2856, 1447, 1062 cm^{-1}. **3b**: δ_H 0.98 (t, 3H, $J=7.3$ Hz), 1.53–1.70 (m, 2H), 2.05–2.26 (m, 2H), 2.13 (brs, 1H), 2.20 (brs, 1H), 2.78 (ddd-like, 1H, $J=2.2$, 5.5, 7.7 Hz), 3.78 (ddd-like, 1H, $J=4.4$, 7.7, 11.0 Hz), 3.90 (ddd-like, 1H, $J=5.1$, 5.3, 11.0 Hz), 4.47 (ddd-like, 1H, $J=2.2$, 5.1, 8.1 Hz); δ_C 10.0, 31.2, 40.3, 45.0, 62.0, 75.6; IR 3354, 2962, 2933, 2877, 1461, 1119, 1049, 961 cm^{-1}. **3c**: δ_H 0.90 (t, 3H, $J=6.4$ Hz), 1.26–1.62 (m, 8H), 2.07–2.25 (m, 2H), 2.37 (brs, 2H), 2.87 (br, 1H), 3.74–4.07 (m, 2H), 4.45 (ddd, 1H, $J=2.2$, 5.1, 8.1 Hz); δ_C 14.0, 22.5, 25.2, 31.6, 38.1, 40.2, 45.5, 62.0, 74.2; IR 3354, 2932, 2869, 1704, 1464, 1050, 653 cm^{-1}.

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