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L-Proline-catalyzed intramolecular cyclization of 5-hydroxypentene to β-halogenated tetrahydrofuran

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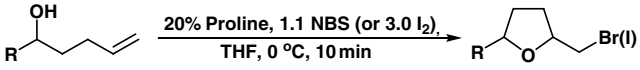
Abstract—A series of β-bromo- and β-iodotetrahydrofurans was synthesized from the reaction mixture of 5-hydroxypentene, L-proline, NBS (or I_2) in THF at 0 °C for 10 min. This L-proline-catalyzed intramolecular cyclization provides a simple and efficient method for the preparation of β-halogenated tetrahydrofuran.

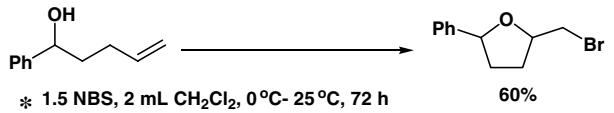
The tetrahydrofuran ring is a very important structural moiety, which is present in a large variety of natural products such as polyether antibiotics.[1–4] The intramolecular alkoxylation reaction, the addition of alcohol onto carbo-carbon multiple bonds, provides an efficient and direct access to tetrahydrofuran functionality.[5] 5-Hydroxypentenes have received much more attention as synthetic intermediates for synthesis of this class of heterocycles.[6–16] The intramolecular cyclization (5-*exo*-trig) of 5-hydroxypentene to tetrahydrofuran ring has been reported and achieved by activation of alkene from halogen[17–20] or Lewis acid,[21,22] epoxidation of alkene followed by intramolecular C–O bond formation,[23–26] and palladium-catalyzed cyclization.[27–29] Halogenated tetrahydrofurans, especially derivatives with an exocyclic bromo- or iodo- functionality located in the β-position to the ring oxygen atom, have become attractive synthesis targets because of the discovery of β-brominated tetrahydrofurans, which were occurred widely as secondary metabolites in the marine environment.[30] The most simple and direct procedure for the synthesis of β-halogenated tetrahydrofurans is the reaction of 5-hydroxypentene with molecular halogen (Br_2, I_2) or halogenating reagent (NBS, IBr, ICl) via intramolecular cyclization (5-*exo*-trig). Herewith, we wish to report a simple and highly efficient method for synthesis of β-bromo and β-iodotetrahydrofuranyl compounds from 5-hydroxypentenes (Scheme 1).



Scheme 1.

5-Hydroxypentenes were prepared by the reaction of 4-bromobutene with aldehydes under a sonochemical Barbier reaction condition.[31] Thus, we firstly investigated the bromocyclization of 1-phenylpentenol with NBS (*N*-bromosuccinimide)[20] at room temperature and β-bromo-phenyltetrahydrofuran was produced in 60% yield after 3 days. The small amount of HBr added to NBS liberates more Br_2 molecule[32] and this reaction condition was investigated for bromocyclization of 1-phenylpentenol. The trace amount of concd HBr (20 μL/equiv) was added to a reaction mixture of 1-phenylpentenol and NBS in CH_2Cl_2 at 0 °C and 96% yield of β-bromo-phenyltetrahydrofuran was obtained after 30 min (Scheme 2). The catalytic amount of HBr promoted the formation yield of β-bromotetrahydrofuran and the reaction time decreased dramatically.

A series of 5-hydroxypentenes was investigated under this HBr-catalyzed bromocyclization reaction condition



Scheme 2.

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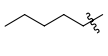
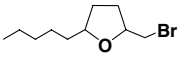
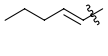
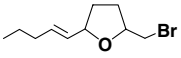
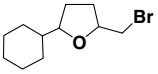
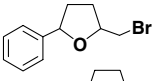
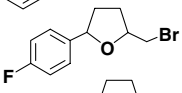
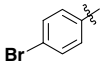
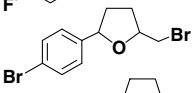
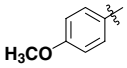
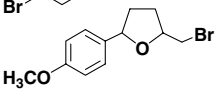
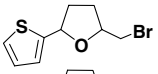
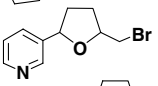
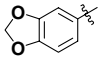
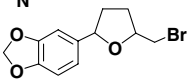
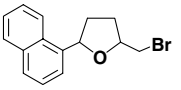
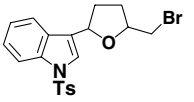
Table 1. HBr-catalyzed bromocyclization of 5-hydroxypentene

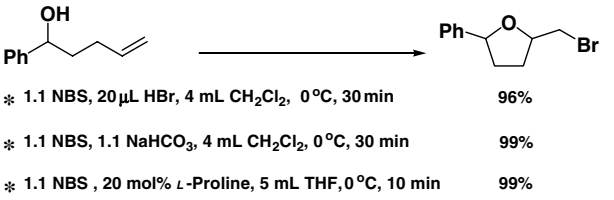
Entry	R	Product	Yield[a] (cis/trans)[b]
1			72% (26:74)
2			88% (44:56)
3			92% (26:74)
4			96% (30:70)
5			95% (32:68)
6			99% (35:65)
7			98% (39:61)
8			75% (40:60)
9			64% (30:70)
10			93% (37:63)
11			99% (37:63)
12			80% (42:58)

[a] The yields were determined after chromatographic purifications.
[b] The cis/trans ratio is determined by ^{1}H NMR spectral analysis.

and the results are shown in Table 1. The typical procedure for synthesis of a β-bromotetrahydrofuran is as follows: To a reaction mixture of 5-hydroxypentene (1.0 mmol) and NBS (1.1 mmol) in CH_2Cl_2 at 0 °C was added concentrated HBr (20 μL). After the reaction mixture was stirred at 0 °C for 30 min, water (10 mL) was added and extracted with ether (3 × 20 mL). The combined organic layer was washed with Brine (30 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexanes.

Good to excellent yields of the investigated compounds in Table 1 were afforded under this HBr-catalyzed reaction condition. The diastereoselectivity (cis/trans) ratios were also determined by ^{1}H NMR spectral analysis. The coupling constant values of 2- and 5-position protons were measured and as reference for the determination of cis/trans ratio.

The addition of HBr catalyzed the bromocyclization of 5-hydroxypentene. Thus, we think the addition of a base may accelerate the cyclization step by deprotonation of alcohol which becomes a better nucleophile to the activated carbon–carbon double bond. The stoichiometric amount of a base such as $NaHCO_3$ was added to a mixture of 5-hydroxypentene and NBS and it was stirred at 0 °C for 30 min (Scheme 3). The introduction of a base improves the reaction rate and yield which presents the same effect as the addition of HBr. Thus, we think the introduction of an amino acid such as proline[33–36] may exhibit the similar improvement for this intramolecular cyclization. To a reaction mixture of 1-phenylpentenol and NBS in THF at 0 °C was added natural proline. The reaction mixture was stirred at 0 °C for 10 min and 99% yield of β-bromo-phenyltetrahydrofuran was obtained. A catalytic amount of L-proline accelerated this bromocyclization of 5-hydroxypentene compound and a high formation yield was also achieved.



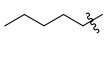
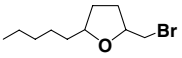
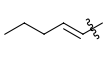
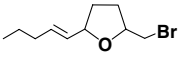
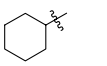
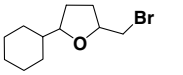
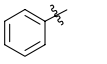
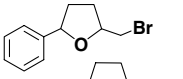
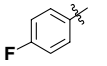
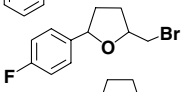
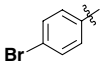
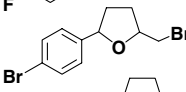
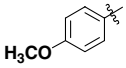
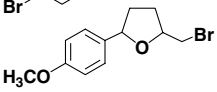
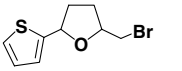
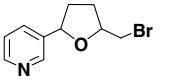
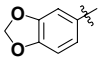
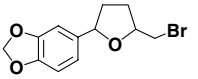
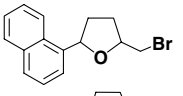
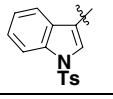
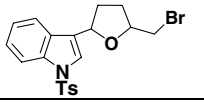
Scheme 3.

A series of 5-hydroxypentenes was investigated under this proline-catalyzed bromocyclization and the results are shown in Table 2. The typical procedure for synthesis of a β-bromotetrahydrofuran in the presence of proline as catalyst is as follows: To a reaction mixture of 5-hydroxypentene (1.0 mmol) and NBS (1.1 mmol) in THF at 0 °C was added L-proline (100 μL, 2 M aqueous solution). After the reaction mixture was stirred at 0 °C for 10 min, water (10 mL) was added, and extracted with ether (3 × 20 mL). The combined organic layer was washed with Brine (30 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexanes.

The yields and stereoselectivities (cis/trans) of β-bromotetrahydrofuranyl compounds, which were obtained from the L-proline-catalyzed reaction conditions, usually are better than the product obtained by HBr-catalyzed cyclization reaction condition. Alkyl-substituted 5-hydroxypentenes afford much higher yields of tetrahydrofuranyl compounds under proline-catalyzed cyclization reaction condition. Heterocyclic tetrahydrofuranyl compounds were easily synthesized under the reaction conditions.

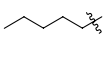
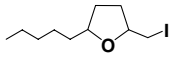
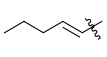
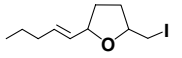
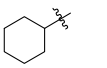
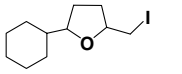
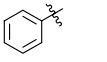
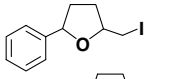
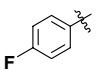
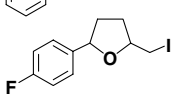
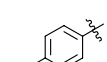
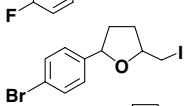
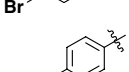
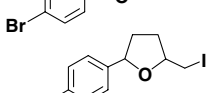
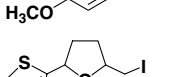
β-Iodotetrahydrofuranyl compounds were typically prepared from the intramolecular cyclization of 5-hydroxypentenes by using I_2 as iodinating reagent. Thus, we investigated the intramolecular cyclization of 1-phenylpentenol with iodine and the expected product was not produced after 24 h (Scheme 4). Another iodinating reagent IBr was also investigated and generated 68% yield of β-iodotetrahydrofuran after 2 h stirring at 0 °C. The β-iodophenyltetrahydrofuran was obtained with a 54%

Table 2. Proline-catalyzed bromocyclization of 5-hydroxypentene

Entry	R	Product	Yield[a] (cis/trans)[b]
1			98% (24:76)
2			94% (30:70)
3			94% (6:94)
4			99% (35:65)
5			99% (28:72)
6			95% (27:73)
7			98% (24:76)
8			94% (30:70)
9			57% (28:72)
10			86% (26:74)
11			99% (27:73)
12			95% (31:69)

[a] The yields were determined after chromatographic purifications.
[b] The cis/trans ratio is determined by ^{1}H NMR analysis.

Table 3. Proline-catalyzed iodocyclization of 5-hydroxypentene

Entry	R	Product	Yield[a] (cis/trans)[b]
1			97% (30:70)
2			88% (34:66)
3			96% (25:75)
4			99% (30:70)
5			93% (23:77)
6			99% (24:76)
7			92% (51:49)
8			76% (36:64)
9			61% (39:61)
10			88% (45:55)
11			98% (22:78)
12			90% (44:56)

[a] The yields were determined after chromatographic purifications.
[b] The cis/trans ratio is determined by ^{1}H NMR spectral analysis.

Scheme 4.

when a base KI was introduced into the reaction mixture. The yield can be increased to 91% when an amount of I_2 and KI were introduced to 3 and 1.5 equiv. An excellent yield (99%) was achieved when a catalytic amount of L-proline was introduced to the iodocyclization reaction condition.

A series of 5-hydroxypentenes was investigated under this proline-catalyzed iodocyclization reaction condition and the results are shown in Table 3. The typical procedure for synthesis of a β-iodonated tetrahydrofuran is as follows: To a reaction mixture of 5-hydroxypentene (1.0 mmol) and I_2 (3.0 mmol) in THF at 0 °C was added L-proline (0.2 mmol) and the reaction mixture was stirred at 0 °C for 10 min. The mixture was quenched with saturated $Na_2S_2O_7$ (10 mL), extracted with ether (20 mL × 3). The organic layer was washed with brine (30 mL), dried with $MgSO_4$, and then removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexanes.

The experimental results showed that the formation yield of β-iodotetrahydrofuran was nearly as high as the yield of β-bromotetrahydrofuran obtained under the reaction condition. The stereoselectivity (cis/trans) of proline-catalyzed bromocyclization reaction generally is better than its corresponding iodocyclization reaction.

In conclusion, this natural proline-catalyzed reaction provides a simple and highly efficient method for the preparation of β-halogenated (β-bromo or β-iodo) tetrahydrofuranyl compound from 5-hydroxypentene via an intramolecular cyclization (5-*exo*-trig) under either acidic or basic reaction condition.

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